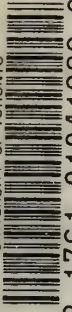


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BIOLOGICAL AND BEHAVIOURAL APPROACHES TO DRUG DEPENDANCE

· Edited by: **H.D. CAPPELL and
A.E. LeBLANC**



**ADDICTION RESEARCH FOUNDATION
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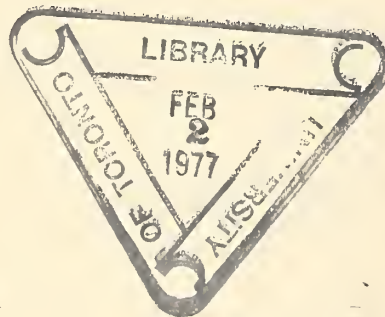


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Preface

Because we have enjoyed the good fortune of having Harold Kalant provide an overview of the material covered in the volume, a preface becomes virtually gratuitous. Yet we would like to say a word about the appropriateness of a symposium that brought together researchers whose work covers everything from biochemical studies of drug dependence to conditioning therapies in alcoholism. In her chapter, Dora Goldstein observed that while it is instructive for investigators to interact with colleagues who take different approaches toward the same final path, each is maximally effective to the extent that he or she pursues an area of special expertise and competence in the actual day to day pursuit of scientific knowledge. We could not agree more fully with this sentiment. Yet it is nonetheless essential to have opportunities to seek and develop connections between laboratory and clinical work, within and between disciplines, at both empirical and conceptual levels; whether we favor biochemicals or biofeedback, it is essential to keep in mind that these pursuits must ultimately have something to do with each other if we are ever to arrest the toll exacted by drug dependence in all its manifestations. Our own view, admittedly biased, was that our understanding of the phenomena of drug dependence was enhanced by the opportunity to speak and listen to the outstanding scientists whose work is represented in these pages. We hope that readers will be able to share this experience indirectly.

H.D.C.

A.E.L.

PARTICIPANTS AND CONTRIBUTORS

HOWARD D. CAPPELL
Addiction Research Foundation
Psychology Department
33 Russell Street
Toronto, Ontario, Canada
M5S 2S1

MIRIAM COHEN
Boston Drug Treatment Program and
Department of Psychiatry
Harvard Medical School
Boston City Hospital
Boston, Mass. 02118
U.S.A.

DAVID A. DOWNS
Department of Pharmacology
University of Michigan
Ann Arbor
Michigan 48104
U.S.A.

GERHARD FREUND
Veterans Administration Hospital
Gainesville, Fla. 32601
and
Department of Medicine
University of Florida School of Medicine
Gainesville, Florida, 32601
U.S.A.

AVRAM GOLDSTEIN
Stanford University Medical Center
Addiction Research Laboratory
Department of Pharmacology
701 Welch Road, Suite 325
Palo Alto, California 94304
U.S.A.

DORA B. GOLDSTEIN
Stanford University Medical Center
Stanford University School of Medicine
Department of Pharmacology
Stanford, California 94305
U.S.A.

HAROLD KALANT
Addiction Research Foundation
Biological Studies
33 Russell Street
Toronto, Ontario, Canada
M5S 2S1
and
University of Toronto
Department of Pharmacology
Medical Sciences Building
Toronto, Ontario, Canada

A.E. LEBLANC
Addiction Research Foundation
Biological Studies
33 Russell Street
Toronto, Ontario, Canada
M5S 2S1

MARK E. LLEWELLYN
University of Michigan
Psychology Department
Ann Arbor
Michigan 48104
U.S.A.

NANCY K. MELLO
Laboratory of Alcohol Research
Saint Elizabeth's Hospital
Washington D.C. 20032
Presently at:
Alcohol & Drug Abuse Research Center
Harvard Medical School
McLean Hospital
Belmont, Massachusetts 02178
U.S.A.

JACK H. MENDELSON*
Department of Psychiatry
Harvard Medical School
Boston City Hospital
Boston, Massachusetts 02118

Presently at:
Department of Psychiatry
Harvard Medical School
The McLean Hospital
A Division of the Massachusetts
General Hospital
Belmont, Massachusetts 02178
U.S.A.

PETER E. NATHAN —
Alcohol Behavior Research Laboratory
Rutgers University
New Brunswick, New Jersey 08903
U.S.A.

STANLEY J. SILVERSTEIN
Haverford State Hospital
Haverford
Pennsylvania
U.S.A.

LINDA C. SOBELL
Orange County (Ca.)
Department of Mental Health Alcoholism
Services
Santa Ana, California 92703
and
University of California
Irvine, California
Presently at:
Dede Wallace (Nashville) Mental Health Center
Vanderbilt University
Nashville, Tennessee 37240
U.S.A.

*The Editors regret that the work presented by Dr. Mendelson could not appear in this volume. Interested readers are referred to the following source, in which the material has been published in substantially similar form:

Mendelson, J. H. and N. K. Mello. "Alcohol, Aggression and Androgens." In: *Aggression. Proceedings of the Association for Research in Nervous and Mental Disease*. S. H. Frazier (ed.) Williams & Wilkins, Baltimore, V.52, 1974, p.225-247.

Special thanks are due Dr. Mendelson for his outstanding intellectual contribution to the symposium.

MARK B. SOBELL
Orange County (Ca.)
Department of Mental Health Alcoholism
Services
Santa Ana, California 92703
and
University of California
Irvine, California
Presently at:
Department of Psychology
Vanderbilt University
Nashville, Tennessee 37240
U.S.A.

JOHN J. STEFFEN
Department of Psychology
Rutgers University
New Brunswick, New Jersey 08903
Presently at:
Department of Psychology
University of Cincinnati
Cincinnati, Ohio
U.S.A.

G. TERENCE WILSON
Department of Psychology
Rutgers University
New Brunswick, New Jersey 08903
U.S.A.

JAMES H. WOODS
Departments of Pharmacology
and Psychology
University of Michigan
Ann Arbor
Michigan 48104
U.S.A.

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Testing the Homeostat Hypothesis of Drug Addiction

Dora B. Goldstein¹

INTRODUCTION

One of E. M. Jellinek's cogent comments on alcoholism research was the following:

The etiquette of the American alcoholism literature demands that the psychiatrist should acknowledge that physiopathological, cultural and social elements have a role in the genesis of alcoholism. On the other hand, the physiopathologist is required to admit the existence of social, cultural and possibly some individual psychological factors. With few exceptions, however, after having made the prescribed bow, specialists proceed to formulate their respective theories exclusively in terms of their respective disciplines.

E. M. Jellinek, *The Disease Concept of Alcoholism*, p. 13.

I share Jellinek's view that investigators in this field should take an interest in many different aspects of alcoholism. However, in the actual designing of experiments it is appropriate for each of us to ask specific questions that can be answered by our own available techniques. The problem of alcoholism is simply too big to encompass all at once. We must break it down into fragments that we are capable of analyzing.

My own bits of this colossal jigsaw puzzle are in the pharmacology section. Alcohol effects, whether acute or chronic, can be studied by the same sorts of pharmacological techniques that are suitable for other drugs. I am interested primarily in physical dependence on ethanol, which can be regarded simply as an effect of chronic drug administration, in the same way that liver damage is. We will study it by delivering the drug to the brain over a period of time and examining the results. For the moment, these results can be expressed in terms of rather crude observations of the withdrawal reaction. When we have learned more about the specific abnormalities that cause the withdrawal reaction, we

¹Department of Pharmacology, Stanford University School of Medicine, Stanford, California 94305, USA.

will be able to study physical dependence much more elegantly with biochemical, biophysical, morphological or other objective assays.

For quantitative pharmacological studies of this type the route of drug administration is irrelevant. What is important is to get the drug to its site of action in known concentrations. Therefore I suggest that we should administer the drug ourselves, rather than leave the matter of drug intake to the discretion of the mice. Control of alcohol levels in the brain is, for my purposes, more important than an attempt to mimic the oral, voluntary consumption of alcohol by human alcoholics. I have no objections to giving the drug by mouth or even voluntarily, provided this does not interfere with my main objective, but I do not feel there is any inherent advantage in such routes of administration. This is a point on which I differ with some of the other designers of animal models.

THE INHALATION MODEL

Continuous Intoxication: Rationale

How could we control the brain level of alcohol in such a way as to produce physical dependence? It seemed reasonable at the start to try to keep a constant amount of alcohol in the brain during the period of intoxication so as to be able to analyze the dose effects in a straightforward way. When I began this experimental work (in 1969), there was already evidence in the literature that maintaining continuous intoxication is the key to producing physical dependence. Isbell and coworkers (1955) had produced undeniable physical dependence in man by administering ethanol at frequent intervals around the clock. Essig and Lam (1968), Ellis and Pick (1970), Deneau, Yanagita and Seevers (1969) and Freund (1969) had devised various methods for keeping animals continuously intoxicated. They had all succeeded in producing syndromes of withdrawal signs similar to those in man. Evidence that intermittent intoxication is relatively ineffective was available from the many studies where alcohol was offered in the animals' drinking water and no withdrawal reactions were observed.

Besides this empirical evidence that continuous intoxication produces physical dependence, we have a hypothesis as to why it should do so. We postulate that drug dependence represents *adaptation*. The presence of the drug at some target structure, presumably in the brain, is a stimulus for a physiological adaptive reaction which in time allows the brain to function well in the presence of the drug and poorly in its absence. On withdrawal, the brain finds itself adapted to a condition that no longer obtains. The resulting imbalance is displayed as the withdrawal syndrome. This "homeostat hypothesis" has been reformulated several times since Himmelsbach (1943) first brought it up in relation to neuronal adaptation to opiates. Several specific mechanisms for the adaptation have been suggested. Martin (1968) sees it as development of redundant pathways in the brain, Collier (1966) as synthesis of excess receptors, and Avram Goldstein and I (1961, 1968) as well as Shuster (1961) have expressed it in terms of enzyme derepression. None of us has produced any experimental evidence for a specific mechanism.

What is important for the experimental design is the time course implicit in the homeostat hypothesis. It predicts that physical dependence should arise rather rapidly, in accordance with the time courses of known physiological regulatory mechanisms. Its half-time should be a matter of hours or days, not the years or decades that used to be considered necessary for the development of drug addiction. This is surely testable. What is needed is to apply the stimulus constantly and measure the amount of dependence that

has developed. If adaptation is rapid, return to normal will also be a matter of hours or days. This predicted rapidity of adaptation and de-adaptation explains why we want to maintain continuous intoxication. If the degree of intoxication were allowed to fluctuate, the adaptation might proceed so irregularly that its time course could not be measured and indeed it might never build up to observable magnitude.

Methods

Maintaining continuous intoxication. Our method for maintaining constant blood alcohol levels involves administration of alcohol to mice by inhalation. Mice are simply housed in an atmosphere of dilute alcohol vapor and are injected daily with a small dose of pyrazole, an inhibitor of liver alcohol dehydrogenase that serves to stabilize the blood alcohol concentrations. The use of pyrazole of course introduces an unwanted element into the experiments, so let me emphasize here that the results we have obtained are the actions of ethanol, not those of pyrazole. We have shown this in a variety of ways. Pyrazole alone does not produce the signs of physical dependence. Alcohol alone does produce them; we have administered alcohol by inhalation, by injection and by voluntary drinking and have seen the characteristic convulsions of alcohol withdrawal in every experiment where the magnitude and duration of intoxication were similar to those of the inhalation-pyrazole experiments. The whole syndrome of withdrawal signs, including tremor, spontaneous convulsions and death, has been reproduced in inhalation experiments without the use of pyrazole. However, few mice survive such experiments with appropriate blood levels so we have done most of our work with the much more convenient and controllable pyrazole model.

Assessing the withdrawal reaction. Our method for estimating the magnitude of dependence is to score the withdrawal signs. For that purpose, we now use only one sign, which we have found to be reliable and to correlate well with the severity of the whole syndrome as measured by several different signs. This useful sign is a characteristic type of convulsion that can be elicited by picking the mouse up by the tail. The seizure is usually mild but is easily recognizable. Different degrees of severity are readily apparent and are assigned scores of 1 to 4 points according to a standard scheme. These seizures can be repeatedly elicited in the same animal, for example at hourly intervals, so we can use the scores to follow the time course of the withdrawal reaction, as shown in Figure 1. The peak height of such curves is an indication of the maximum intensity of the withdrawal reaction in the particular group of mice, and the area under the curve represents the overall severity and duration. Thus we can express the withdrawal reaction in numerical terms and by extension we have rough estimates of the degree of dependence that the mice have developed during the preceding period of intoxication. Details of our methods for producing and assessing physical dependence in mice have been published (Goldstein and Pal, 1971; Goldstein, 1972).

RATES OF ONSET AND DECAY OF PHYSICAL DEPENDENCE

Onset

To study the rate of onset of physical dependence, we maintained groups of mice at a blood alcohol level of 1.5 to 2.5 mg/ml for different periods of time and measured the peak height of the withdrawal reactions (Goldstein, 1973a). The results are shown in the upper curve of Figure 2. The intensity of the withdrawal reaction increased with duration

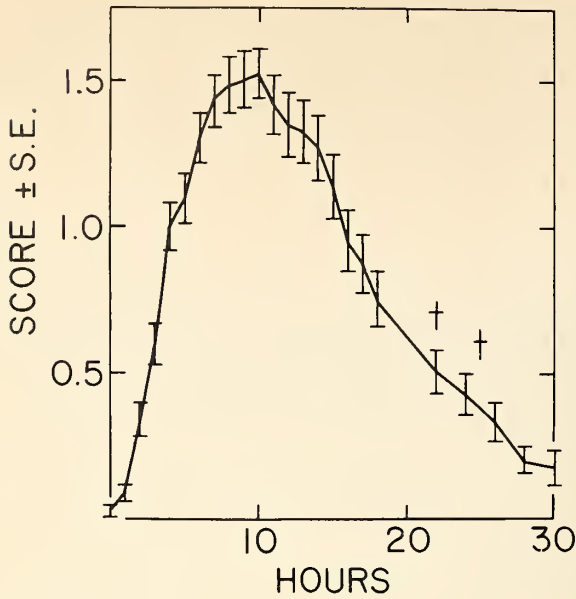


Figure 1. Curve of seizure scores for convulsions elicited by handling during alcohol withdrawal (Goldstein, 1972). Combined results of 11 experiments (95 mice) are shown. Daggers indicate deaths.

of alcohol exposure for at least a week and perhaps two weeks, but was clearly levelling off. Was this plateau an artifact? Perhaps we had reached the ceiling of our scoring method so that further increments in the biochemical dependence could not increase the severity of the elicited convulsions. To check this, we repeated the experiments at a lower

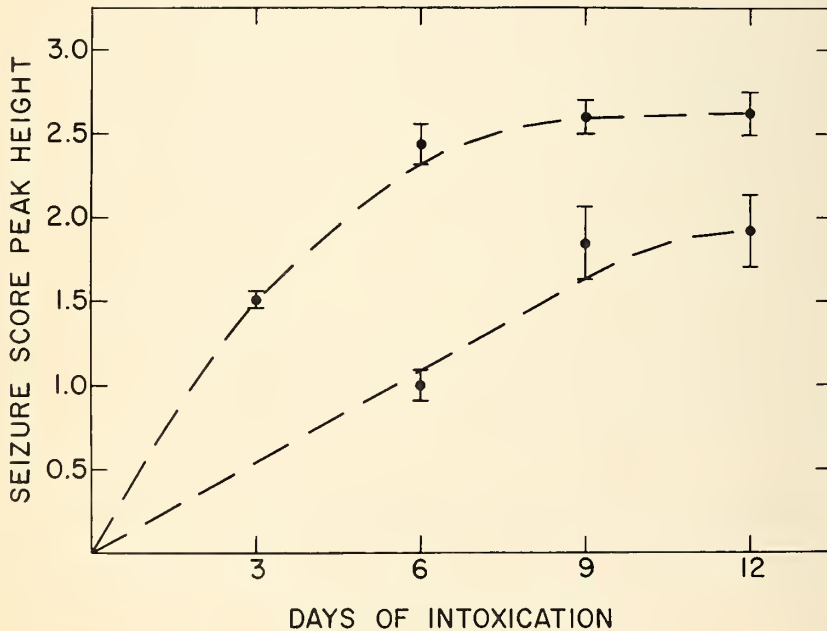


Figure 2. Time course of onset of physical dependence. Mice were exposed to alcohol vapor continuously for the time shown on the abscissa. On withdrawal, the peak height of the withdrawal seizure scores was determined. The points are means; vertical bars indicate standard errors for 9 to 19 mice per group. The blood alcohol levels in the two series were 1.5 to 2.5 mg/ml for the upper curve and 0.5 to 1.5 mg/ml for the lower curve.

blood alcohol concentration, 0.5 to 1.5 mg/ml, with the results shown in the lower curve of Figure 2. Again the scores levelled off between one and two weeks of alcohol intoxication. It appears that at a given blood alcohol level there is a maximum amount of dependence that will ever occur. This is consistent with the view that the blood alcohol level is the stimulus for an adaptive change. The adapting system shifts to a new level of activity and the magnitude of the shift is related to the intensity of the stimulus, *i.e.*, the drug concentration.

Decay

Next we examined the rate of decay of physical dependence and found it to be much faster than the rate of onset. Whereas onset was apparently complete in two weeks, recovery was complete in about one day. The design of the experiments on rate of recovery is shown schematically in Figure 3. We exposed mice to several successive cycles of intoxication, shown by the shaded bars on the time axis. Each cycle consisted of 3 days intoxication at blood alcohol levels of 2 mg/ml. Between cycles the mice were removed from the vapor box for a given interval of time. The aim was to see whether the dependence accrued during the first cycle would carry over into the later cycles and thus give rise to higher withdrawal scores in successive cycles. The upper part of the figure shows what would be expected if the interval between cycles was sufficient to allow complete decay of the dependence. The withdrawal reaction in later cycles would be no more severe than after the first cycle. On the other hand, if the interval was too short for complete recovery, as in the lower diagram, some dependence would persist through the interval and the observed withdrawal scores would cumulate in successive cycles.

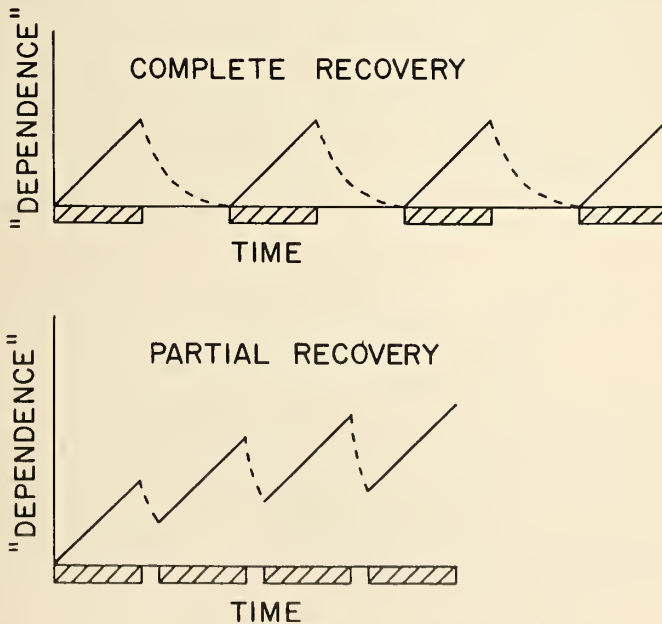


Figure 3. Diagram of "recycling" experiments to measure the decay of dependence. Shaded blocks represent cycles of exposure to alcohol inhalation. The upper section shows a long interval between cycles, with complete decay of dependence. The lower section shows a short interval, with cumulation of dependence in successive cycles. The magnitude of "dependence" can be estimated at the end of each cycle by scoring the withdrawal reaction.

In a series of such "recycling" experiments, we varied the interval between cycles from 0 to 24 hours. What we are here calling a "zero hour interval" is in fact the same set of data cited above, where intoxication was continuous for 3, 6, and 9 days. This is the same as running 1 to 3 cycles (each cycle lasting 3 days) with no interval between cycles. The results of the recycling experiments are best presented by comparing the withdrawal reactions in the first and third cycles (Figure 4). We can express the severity of withdrawal reactions either as peak height or as area under the seizure score curve and calculate the ratio of third cycle to first cycle scores. A high ratio means that the withdrawal reaction was more severe in later cycles, presumably because the interval between cycles was insufficient to allow complete decay of dependence. This is what happened when the interval was 0, 3, 8, or 12 hours, but clearly the extent of cumulation was decreasing over this series, as the ratios were falling. When the interval between cycles was 24 hours, the ratio was close to one, meaning that the later cycles were no more severe than the first and indicating that dependence decayed almost completely in 24 hours.

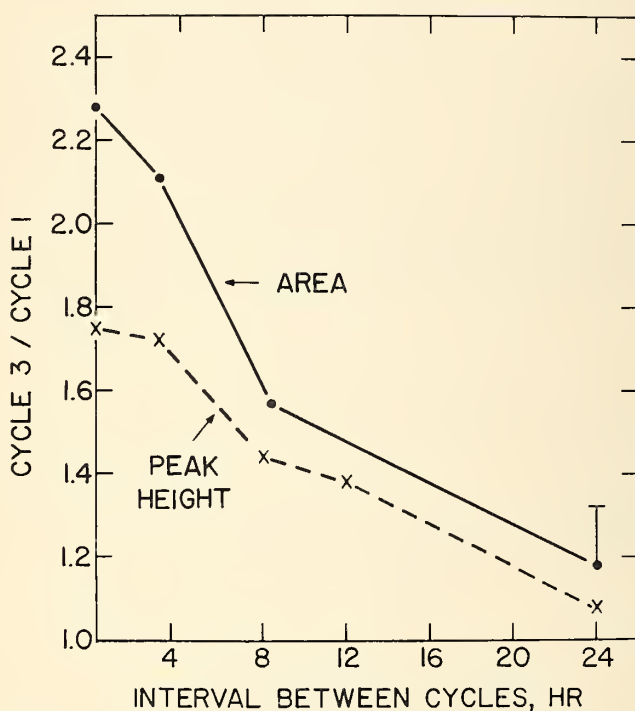


Figure 4. Time course of decay of physical dependence. Mice were given 3 cycles of alcohol treatment, each cycle being 3 days at blood alcohol levels of 1.5 to 2.5 mg/ml, maintained by inhalation. The interval between cycles was varied, as shown on the abscissa. After each cycle, the withdrawal reaction was observed. The points represent the peak scores or the areas under the withdrawal-score curves for the third cycle divided by the first cycle. Groups of 8-12 mice were used for each point, except for the 12-hr interval, where 28 mice were used.

Significance of Rapid Decay

These results bear out my initial preconception that continuous intoxication is necessary for reliable development of physical dependence. Even a few hours of sobriety prevents

the buildup of dependence. This, I believe, explains why it is difficult to demonstrate physical dependence in animals that are given alcohol in their drinking water. We know that rats and mice drink mostly at night, so they will have at least 12 hours to sober up each daytime. The very small quantum of dependence that has built up each night will be partially lost the next day and may never accumulate to levels that will produce an observable withdrawal reaction. Extending the duration of the alcohol administration may not help either. If decay of dependence is a first-order process, as seems reasonable, then the amount lost each daytime will increase as the magnitude of dependence increases, and this will cause the dependence to plateau after several cycles.

(Assume that each night's drinking produces an amount of dependence designated as D_1 . Each daytime a fraction f of the previously accumulated dependence decays. Let $1 - f = a$, the fraction that survives to the next night. After 2 days and nights, the accumulated dependence, $D_2 = D_1 + aD_1 = D_1(1 + a)$. After 3 days and nights, $D_3 = D_1 + aD_2 = D_1(1 + a + a^2)$, and after n such cycles, $D_n = D_1(1 + a + a^2 + a^3 \dots + a^{n-1})$. The sum of such a series is $D_n = \frac{D_1(1-a^n)}{1-a}$ or as n becomes large $D_n = \frac{D_1}{f}$. If half the dependence decays each day, the final level will be only twice the dependence that accumulated the first night, and over 90% of the final level will be attained in 4 days.)

Time Courses in the Withdrawal Period

It is interesting to compare the time courses of the various processes that we can measure during the withdrawal period. These are shown diagrammatically in Figure 5. After removal of mice from the vapor chamber, it takes about 5 hours for the elimination of ethanol from the blood (under the usual conditions with a final blood alcohol level of 2 mg/ml and the final dose of pyrazole at 24 hours before withdrawal). Physical dependence has just about disappeared at 24 hours after withdrawal, as shown above. The time course of the withdrawal reaction itself is also shown here. The scores are zero on withdrawal, when the mice are still intoxicated, and they increase for about the next 10 hours, returning to zero at approximately the same time as does the apparent dependence. It looks as if the end of the overt withdrawal reaction is a fair measure of the complete decay of depen-

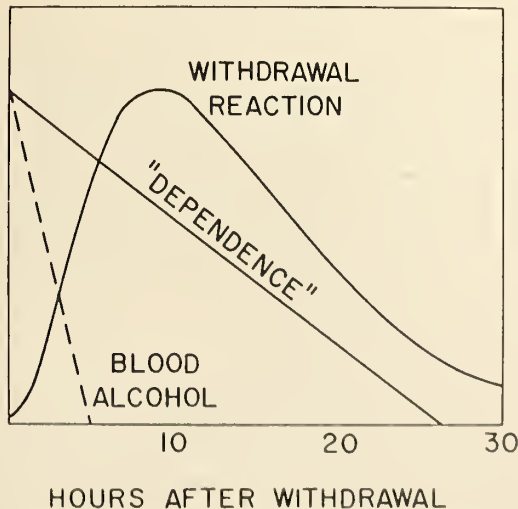


Figure 5. Diagram of time courses during the withdrawal period.

dence. There is a discrepancy, however, between the alcohol disappearance and the peak of the withdrawal reaction. Although the alcohol is gone by 5 hours, the withdrawal signs continue to increase for 5 more hours. One can make up hypotheses to explain this delay in appearance of the peak scores. It might be the time required for a change in the cell body to express itself at the synapse, *i.e.* the time for axonal transport. In quite a different context, Knapp and Mandel (1972) showed that it took several hours for inhibition of tryptophan hydroxylase in the raphe nuclei to be expressed as a fall in serotonin levels of the corresponding nerve terminals. They suggested that slow axonal transport could account for the delay. Alternatively, there might be a slower exit of alcohol from its real site of action, presumably in the interior of membranes, than from the blood, so the time of maximum scores would be the time when the adapting system itself is free of the drug. I am not ready to speculate on these possibilities, but I want to point out that this sort of delay is characteristic of alcohol withdrawal in man as well as in mice. We know from careful clinical observations by Victor and Adams (1953) and others that there is a characteristic sequence of withdrawal signs, some of which peak long after the alcohol is gone. We may imagine that each of the components of the withdrawal reaction has its own mechanism and its own time course. Had we chosen to score withdrawal signs other than convulsions on handling, we might have seen different time courses. A single biochemical derangement, which we call "the dependence", might give rise to a sequence of specific withdrawal signs, each with its own characteristic delay.

NATURE OF THE ALCOHOL TARGET

Mathematical Formulation

Several years ago Avram Goldstein and I developed mathematical models to describe the adaptation hypothesis. They were based on the equations for steady state levels of any compound that is synthesized at a constant rate and breaks down with first order kinetics (Goldstein, Aronow and Kalman, 1968).

$$\frac{dX}{dt} = S - kX$$

where S is the linear rate of synthesis of a compound X , and k is its first-order decay constant. There normally exists a steady state level of X where $dX/dt = 0$ and $X = S/k$. A sustained change in either the rate of synthesis or the rate of breakdown of X will cause its level to rise or fall and eventually to reach a new steady state level determined by the new values of S and k . The time course of such shifts can be shown to depend only on the breakdown rate of X , not on its rate of synthesis. The half-time of the shift is the time required for the level of X to reach halfway to its new steady state level while the new value of k obtains. It is simply $t_{1/2} = \frac{\ln 2}{k}$.

We postulate that during the development of drug dependence there is a drug-induced change in either the rate of synthesis or the rate of breakdown of a hypothetical target compound, X (the adapting system). This will cause a shift in the level of X and we can very roughly determine its time course by our withdrawal seizure scores (since the scores represent the magnitude of dependence). What we need first is an estimate of the time course of the recovery from dependence, because this represents a shift that occurs

under conditions where the drug is not present and both S and k have returned to their normal values. So we can use the time course of recovery to estimate the turnover rate of the adapting system. Our data on decay of alcohol physical dependence in mice show that this process has a half-time of a few hours.

Now we can look at the rate of onset of dependence and see whether it also occurs in a few hours. If so, the rate of target breakdown has not been affected by the drug. This is not what we found. We observed that the onset of dependence was much slower than its decay. This indicates that the breakdown of X was slower than normal during the development of dependence. The data are consistent with the idea that the drug raises the level of the hypothetical target system by stabilizing that system. On withdrawal the system returns to its usual turnover rate and de-adapts rapidly.

We cannot go much further in speculating on the alcohol target except to note that it is reasonable to assume that it is a membrane or resides within a membrane. There is strong evidence that anaesthetics, including aliphatic alcohols, act by entry into biological membranes (Seeman, 1972). It is therefore our guess that alcohol dependence arises because some membrane component is stabilized by the alcohol.

Membrane ATPase

We have made one direct attempt to identify this target (Goldstein and Israel, 1972). Yedy Israel had shown that the Na, K-activated ATPase of rat brain was inhibited by ethanol and also that it increased in activity after chronic ethanol administration. This was the behavior expected of the target. But it is difficult to measure physical dependence quantitatively in rats, so Israel and I used the inhalation system with mice to test this notion. The results were negative. There was no change in activity of mouse brain Na,K-activated ATPase either at the end of the intoxication period or at the peak of the withdrawal reaction.

Neurotransmitters

We have also made a much less direct attempt to identify the target, using the neuropharmacological agents that are known to affect the synthesis, release or postsynaptic action of various neurotransmitters. We measured the effects of these agents on the mouse withdrawal reaction, again using the inhalation system to evoke physical dependence (Goldstein, 1973b). Drugs aimed at γ -aminobutyric acid (GABA) or catecholamines clearly modified the withdrawal reaction, but drugs that affect acetylcholine or serotonin did not. Raising brain GABA levels with aminooxyacetic acid (an inhibitor of GABA transaminase) suppressed the seizures while picrotoxin, which may be a specific GABA antagonist, made the withdrawal convulsions more severe. Interfering with catecholamine systems also increased the seizure scores. We used α -methyltyrosine, reserpine, phentolamine, propranolol and chlorpromazine. All had the same qualitative effect, although their potency and duration of action differed. Reserpine was by far the most dramatic. I interpret these results to mean that some brain excitatory system, apparently not cholinergic, is overactive during the withdrawal period and that neuronal systems utilizing GABA or catecholamines antagonize this hyperexcitability. It is not known whether it is the excitatory or inhibitory pathway that is the actual alcohol target.

SUMMARY

We have used the alcohol inhalation model to collect evidence about the homeostat hypothesis of drug addiction. Our findings so far fit well into the conceptual framework of the hypothesis. We find that, as with other physiological adaptations, the magnitude of change is related to the intensity and duration of the stimulus and that the stimulus must be applied continuously in order to keep the adaptive process in motion. The time course of the adaptation is similar to that of known physiological processes. It can decay in a matter of hours. The data suggest that some brain component is stabilized during the intoxication and then breaks down at its usual rapid turnover rate after removal of the ethanol. The biochemical result of the adaptation appears to involve either the buildup of a neuronal excitatory system or the decline of an inhibitory one. GABA or one of the catecholamines may be the transmitter for the inhibitory pathway. What is needed now, of course, is to identify the actual adapting system. This putative target should respond to drug concentrations and to time in the same way as does the dependence that we now measure indirectly with withdrawal convulsions.

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Animal Models of Ethanol Withdrawal Syndromes and Their Relevance to Pharmacology

Gerhard Freund¹

INTRODUCTION

A subcommittee of the World Health Organization has defined alcoholism as drinking alcohol to an extent that it interferes with physical health, mental health, or function in society (World Health Organization, 1952). The progression from psychological to physiological drug dependence and finally physical and mental deterioration has also been included in that definition (World Health Organization, 1952, National Council on Alcoholism, 1972). It is evident that an animal model that includes all of these facets simultaneously does not exist and probably can never be developed (Lester and Freed, 1973). The psychological (Partington and Johnson, 1969; Rohan, 1972) and social conditions (Cisin and Cahalan, 1971; Robins and Guze, 1971) that may favor the development of excessive ethanol consumption by man are diverse and complex. It is doubtful that such complexity and diversity could ever be simulated in animal models even if drug-seeking behavior leading to pharmacological addiction may be induced. However, certain consequences of excessive ethanol consumption, particularly pharmacological and physiological ones, can be investigated in animals in ways that would be impossible or unethical to study in man. For instance, there is no reason to believe that animal models are less important for the development of prophylaxis or improved therapy of withdrawal syndromes than they are for the development of antibiotics, diuretics, contraceptives, anti-hypertensives or mood-altering drugs.

The *relevance* of animal models to alcohol withdrawal in man is supported by four types of evidence: first, the similarity of the symptomatology (tremors and seizures) in a wide variety of species such as mice, rats, dogs, monkeys, and man as reviewed by Mello

¹Department of Medicine, University of Florida School of Medicine and Veterans Administration Hospital, Gainesville, Florida.

(1973). Second, the same therapeutic agents that are effective in the treatment of alcohol withdrawal in man, are also effective in the treatment of alcohol withdrawal in several animal species (Essig and Lam, 1968; Essig, 1972; Ellis and Pick, 1970; Goldstein, 1972). Third, withdrawal syndromes may be induced in animals with the same drugs (including opiates and barbiturates) known to cause physiological dependence and withdrawal in man (Deneau, Yanagita and Seevers 1969; Essig, 1972; Freund, 1971; Seevers and Deneau, 1963). Finally, electroencephalographic changes (spikes and slow wave discharges) during withdrawal are identical in man and experimental animals (Guerrero-Figueroa, Rye, Gallant, and Bishop, 1970; Isbell, Fraser, Wikler, Belleville and Eisenman, 1955; Wikler and Essig, 1970; Hunter, Walker, Boast and Zornetzer, 1973; Walker and Zornetzer, 1973). It appears reasonable to conclude that the pathogenesis of ethanol withdrawal syndromes at the cellular or subcellular level of biological organization is probably similar or identical in all animal species, including man.

TYPES OF ANIMAL MODELS

Historically, the conditions necessary for the induction of physiological drug dependence and withdrawal were delineated first for opiates (Seevers and Deneau, 1963). These conditions include the administration of adequate amounts of drug for sufficiently long periods of time and at intervals frequent enough to permit continuous exposure of the nervous system. This objective has been difficult to achieve with ethanol because experimental animals do not voluntarily drink adequate amounts of aqueous ethanol solutions (Freund, 1970). Other modes of ethanol administration have used intravascular catheters, gastric intubation, either by means of surgery or oral gavage, or inhalation as reviewed by Mello (1973). Alternatively, animals may be induced to drink ethanol-containing liquids by gradually increasing ethanol concentrations in liquids masking the taste of ethanol (Fitzgerald and Barfield, 1968; Cressman and Cadell, 1971), incorporation into liquid diets (Freund, 1969; Pieper, Skeen, McClure and Bourne, 1972), or behaviorally induced polydipsia (Falk, Samson and Winter, 1972). Adjunctive procedures include slowing of the rate of ethanol metabolism by pyrazole (Goldstein and Pal, 1971), or by weight reduction (Freund, 1969, 1971; Ogata *et al.*, 1971), or increasing the rate of metabolism of nonethanol-derived calories in the liquid ethanol diet by cold exposure (Freund and Walker, 1971; Freund, 1973). The use of an audiogenic stimulus to induce seizure at will during withdrawal in mice normally resistant to audiogenic seizure (Freund and Walker, 1971) has been helpful in therapeutic drug evaluation studies where the duration of drug effect is to be determined (Freund, 1973).

The previously published method for inducing ethanol withdrawal signs in mice (Freund, 1969) was recently modified. To prevent clogging of standard 8 mm outer diameter (O.D.) stainless steel drinking tubes, with dried, liquid diet membranes, the conical end was cut off so that the tubes had a uniform inner diameter (I.D.) of 6.5 mm throughout. Bending of the tubes to an angle of 100° and leaving the nearly horizontal, slightly downward sloping portion of the drinking tube to protrude 3 cm from the vertical stem, prevented the liquid diet from escaping from the vertically positioned liquid diet reservoir (rubber-stoppered bottle or sawed off graduate cylinder) and prevented a retraction of the liquid meniscus into the tube. During intoxication mice had difficulty reaching the drinking tube unless the opening was approximately 3 cm above the cage floor. Mice were reduced in weight by daily feedings of weighed portions of guinea pig chow

pellets and subsequent feeding of chocolate flavored Metrecal-shape (Mead-Johnson, Evansville, Indiana) liquid diet containing 35 per cent of calories in the form of ethanol (or stock solution containing 12.8 ml of 63% v/v 95% ethanol in distilled water, Metrecal to 100 ml TV) as described previously (Freund, 1970). The diet was changed daily although storage of freshly prepared diets in a refrigerator is possible for 3 days without deterioration. All dietary equipment was sterilized after each use. All experiments were carried out at room temperature with C57BL/6J female mice of age 3-4 months, weighing 20.0 to 23 g. Older, smaller or genetically different mice were found to have a statistically significant lower incidence and severity of withdrawal signs. Mice were housed individually in clear 12 x 7 x 5 inch polycarbonate cages (Carworth, New York) divided into 4 equal compartments with removable, clear plexiglas dividers. The drinking tubes were inserted through the top of a flat wire bar cover with the opening pointing upwards during insertion in order to minimize spillage. The audiogenic stimulus was applied seven hours after the beginning of ethanol withdrawal at approximately 2:00 p.m. as previously described (Freund and Walker, 1971). The stages of withdrawal (Freund, 1969) briefly are: stage I tremors; II severe tremor, sudden sprawling with opisthotonus and tail arching forward over snout; III convulsions; IV death during convulsion. The effects of varying the degree of weight reduction and duration of ethanol consumption are shown in the Table.

TABLE I

EFFECT OF WEIGHT REDUCTION AND DURATION OF ETHANOL CONSUMPTION
ON THE SEVERITY OF WITHDRAWAL SIGNS AT ROOM TEMPERATURE

Lab Chow 1.0 g/day (x days)	Body Weight Loss (g)	Ethanol Diet (x days)	Body Weight Change* ± (g)	Maximal Stage of Withdrawal (number of mice)							
				0	Spontaneous				Audiogenic		
					I	II	III	IV	III	IV	
2	-2.1 ± 0.1	6	+ 0.4 ± 0.3	0	2	14	0	0	1	7	
2	-2.3 ± 0.2	5	+ 0.8 ± 0.2	0	1	15	0	0	2	3	
2	-1.9 ± 0.4	4	+ 1.0 ± 0.1	0	8	8	0	0	2	4	
3	-2.8 ± 0.6	4	+ 0.7 ± 0.2	1	7	8	0	0	3	1	
4	-2.8 ± 0.2	4	+ 1.0 ± 0.2	1	7	8	0	0	2	1	
5	-3.5 ± 0.2	4	+ 1.3 ± 0.1	1	8	7	0	0	1	3	
2**	-2.9 ± 0.2	5	+ 0.1 ± 0.4	0	8	8	0	0	6	6	
2**	-2.9 ± 0.2	6	+ 0.8 ± 0.3	0	4	12	0	0	6	6	
4**	-4.1 ± 0.2	6	+ 0.3 ± 0.4	0	2	14	0	0	14	2	
4**	-3.5 ± 0.3	7	+ 0.1 ± 0.4	0	8	8	0	0	2	4	

* During ethanol consumption

**No food during the first 24 hours preceding 1.0 g chow/day

Note: There were 16 C57BL/6J female 20-22 g, 3-4 months old mice in each group, fed 1.0 g of guinea pig chow pellets/mouse/day followed by feeding a liquid diet containing 35% of calories derived from ethanol. Values are expressed as mean ± S.E. Audiogenically (bell ringing) induced seizures recorded 7 hours after the beginning of withdrawal in survivors of spontaneous withdrawals.

The results indicate that a high yield of ethanol withdrawal signs can be obtained with slight body weight reduction of 10 - 15 per cent, a range customary for nearly all food-motivated behavioral learning tasks and often maintained for many months without evidence of nutritional impairment. The same liquid ethanol diet has been previously

administered to mice and rats for many months without evidence of nutritional impairment (Freund, 1970; Freund and Walker, 1971; Walker and Freund, 1971). In contrast to previous experiments (Freund, 1969, 1970) the high ethanol preference mouse strain C57BL/6J was used. This may explain why body weight *gain* was observed while the animals consumed the ethanol diet in this experiment. This has also been observed by Walker and Zornetzer (1973). These findings and the observation that a few mice occasionally have spontaneous withdrawal reactions while consuming this diet over a period of months and while gaining weight (Freund, 1973) make it improbable that malnutrition plays a significant role in the pathogenesis of the withdrawal syndrome in mice. The purpose of initial weight reduction is merely to increase food consumption and to decrease the rate of ethanol metabolism (Freund, 1973).

Quantification of Withdrawal Signs

In the simplest form of rating the severity of withdrawal, the presence or absence of tremors, sudden sprawling movements with opisthotonus, tail signs and various types of seizures (including death during seizure) have been recorded (Freund, 1969). More elaborate additive point scores have been devised (Goldstein and Pal, 1971). The inducibility of seizures by means of an audiogenic stimulus has been introduced (Freund and Walker, 1971). The quantification of tremors, however, has been difficult.

The following previously unpublished method for the recording of withdrawal tremors in mice was developed in this author's laboratory. Mice were housed individually in 16 oz. clear styrene containers (Laboratory Supplies Co., Hicksville, New York) weighing 26 g. For recording sessions this container was attached to a lid that was suspended from the stylus of a Harvard Model 386 Heart/Smooth Muscle Transducer 1.5 cm from the center of the stylus (Harvard Apparatus Co., Millis, Mass.). The stylus was suspended 7.5 cm from the center with a rubber band hanging from an adjustable buret clamp. This permitted centering of the transducer stylus (and recording pen) by turning the thumb screw of the buret holder with the "offset" dial in the central position. This made possible later minor adjustments of the pen centering with the "offset" dial only. The vibrations were recorded with a Harvard Model 350 Electronic Recording Module mounted on a Harvard Chart Mover. The paper speed was 0.5 or 0.25 cm/sec. The sensitivity was standardized by adjusting the "Gain" dial so that a 20 g weight placed on top of the cage lid resulted in a deflection of 2.0 cm from the baseline. Several animals were recorded simultaneously (controls and treated) on separate channels. Spontaneous movements, tremors and seizures can be easily distinguished on the record by their frequency and amplitude. The frequency, duration and amplitude of tremors and seizures can be measured (Figures 1 and 2). The only movements that presented difficulties in distinguishing on the record from mild tremors were vigorous grooming movements. However, mice during the first 8 hours after ethanol withdrawal show only few spontaneous movements and rarely grooming.

Pathogenesis of Withdrawal Syndromes

The pathogenesis of withdrawal syndromes is essentially unknown if pathogenesis is defined as an orderly series of events beginning with specific molecular interactions leading to the overt clinical syndrome. However, several working hypotheses at all levels

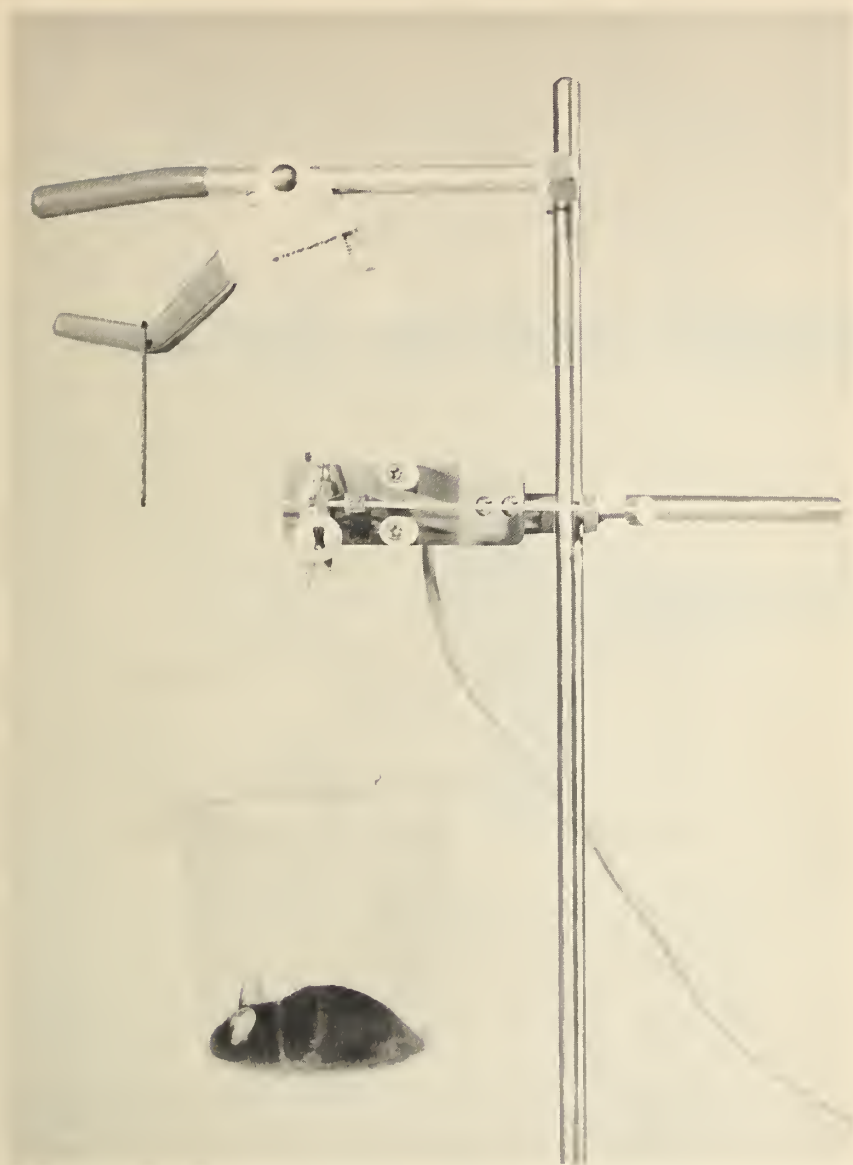


Figure 1. *Recording of tremors and convulsions in mice with Harvard model 386 Heart/Smooth Muscle Transducer. During withdrawal, mice are housed individually in polystyrene containers that may be attached to plastic lid suspended from stylus for recording.*

of biological organization are being explored (Seevers and Deneau, 1963; Wikler, 1968; Schuster and Thompson, 1969; Dole, 1970; Pharmacology Society Symposium, 1970; Mendelson, 1971, Wikler, 1972).

Anatomical Considerations

It is conceivable that the clinical signs of nervous system overactivity, ranging from tremulousness to generalized tonic-clonic convulsions, are the result of a "rebound" from

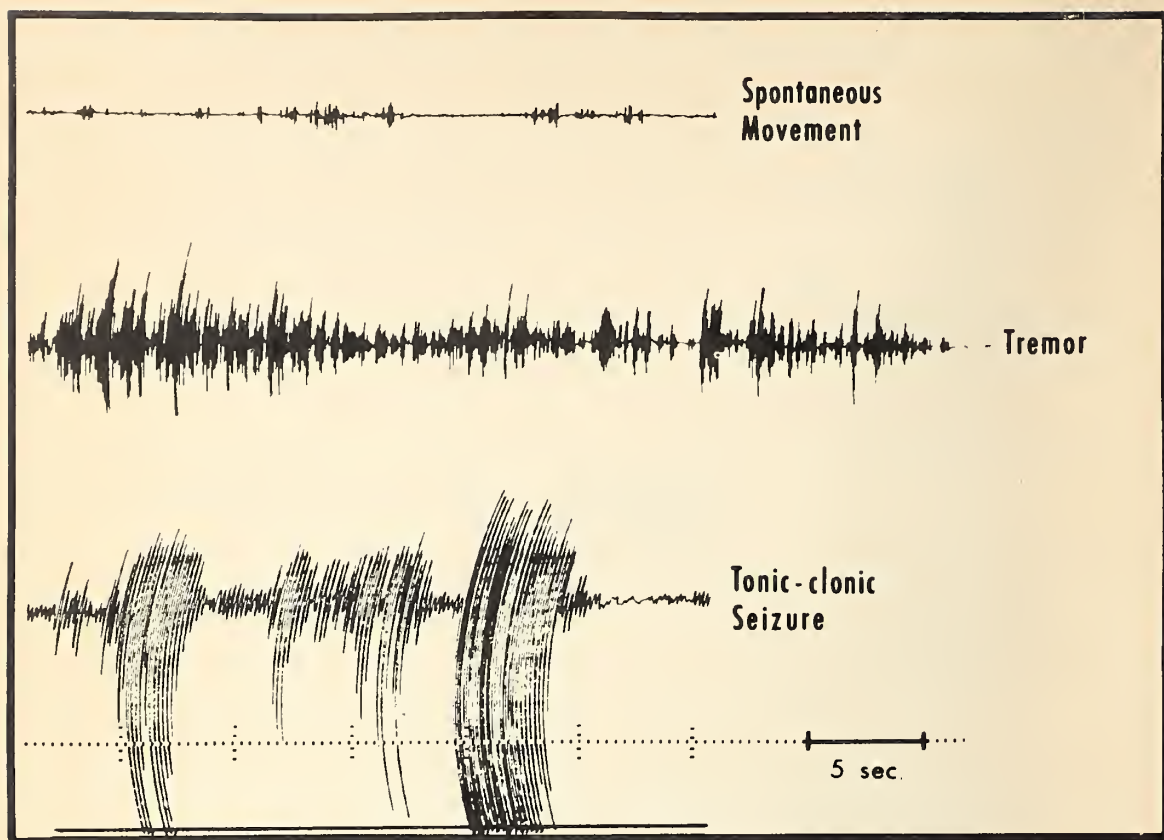


Figure 2. Paper recording with Harvard Electronic Recording module of ethanol withdrawal signs of a mouse. Mechanical vibrations are transmitted from a mouse in a light-weight plastic cage suspended from the stylus of a heart/smooth muscle transducer.

previous pharmacological depression. At the cellular level this may be related to deafferentation or disuse hypersensitivity (Sharpless, 1969). Other hypotheses assume the mobilization of alternate, normally inactive, neuronal pathways (Martin, 1970). This hypothesis may perhaps be supported in opiate withdrawal by the findings that withdrawal signs may be ameliorated by stereotactic, localized hypothalamic lesions (Kerr and Pozuelo, 1971) but not limbic lesions (Wikler, Norrell and Miller, 1972). Other investigators found that lesions in several other subcortical brain regions caused amelioration of withdrawal signs as well and concluded that a combination of brain structures appear to be necessary for the development of opiate addiction (Little, Robinson, D'Encarnacao and D'Encarnacao, 1973). Opiate withdrawal can be precipitated by localized application of antagonists into the thalamus and to a lesser extent into other brain regions (Wei, Loh and Way, 1972) or by injection into the fourth ventricle and not the more anterior parts of the ventricular system (Herz, Teschemacher, Albus and Ziegelgaensberger, 1972).

The active participation of subcortical structures in epileptiform activation (Marsan, 1972) would make it plausible that seizure activity and threshold or other CNS manifestations of withdrawal can be modified by ablations in a more or less specific way. Electrical stimulation of *lateral* hypothalamic regions decreases cortical penicillin-induced epileptiform activity and *medial* stimulation enhances it (Isaacson and Gage, 1973). The *depletion* of norepinephrine (NE) in subcortical regions enhances the spreading of audio-genic seizures from brain stem "oscillators", whereas spreading is inhibited by *increased*

NE (Jobe, Picchioni and Chin, 1973). The depletion of subcortical neurotransmitters (norepinephrine, dopamine and serotonin) generally facilitates seizures induced by convulsants or electroshock and raising their concentrations suppresses seizures (Wenger, Stitz and Craig, 1973; Kilian and Frey, 1973). Whether the effects of localized ablations and electrical stimulations or alterations of neurotransmitter metabolism on withdrawal signs are specific or not, it is conceivable that the clinical expression of withdrawal (e.g. type of seizure) could be the result of a preferential physiological or biochemical affinity of particular addicting agents to specific brain structures or regions.

Biochemical Aspects

At the biochemical level of organization a corollary to the mobilization of normally inactive pathways might be an activation of postsynaptic, normally "silent receptor sites" by the addictive drug (Collier, 1965) or of presynaptic transmitter – synthesizing enzyme induction (Goldstein and Goldstein, 1968; Shuster, 1961). Whatever primary mechanisms may be operative, the resulting changes of substrate concentrations or turnover rates, or both, could secondarily affect every aspect of cell metabolism and function. However, it is probable that the chemical reactions most closely related to the generation, conduction, and transmission (through synaptic membranes) of action potentials are very important for the pathogenesis of withdrawal signs. But the demonstration of changes in neurotransmitter turnover rates alone does not in itself prove a primary pathogenetic significance (Ehrenpreis and Teller, 1972) because these changes may be a result, concomitant or prerequisite, rather than the cause of withdrawal seizures.

Because of the lack, until recently, of animal models for ethanol withdrawal syndromes, little is known about the biochemical changes in the nervous system during ethanol withdrawal. It was therefore of great interest when a unitarian concept for physiological dependence on alcohol and opium was suggested (Davis & Walsh, 1970). Acetaldehyde, the only metabolite specific for ethanol, was found to form opium-like alkaloids from catecholamine precursors in the brain (Davis and Walsh, 1970) and adrenal gland (Cohen and Collins, 1970). However, the role of an endogenous opium alkaloid as the cause of ethanol dependence has been questioned for several reasons, particularly because of the absence of cross-dependence between opiates and ethanol (Seever, 1970; Halushka and Hoffman, 1970; Goldstein and Judson, 1971). As discussed by Gitlow (1973): there can be no conversion of catecholamines to opioids induced by other addicting drugs (e.g. barbiturates) because they are not metabolized to acetaldehyde or formaldehyde²; the development of tolerance to opioids is extensive and to ethanol minimal; shunting of catecholamine metabolism from oxidative to reductive catabolic pathways by drugs other than ethanol (disulfiram) does not cause physical dependence; the concentrations of aldehydes needed to form opioids *in vitro* are appreciably above the concentrations encountered *in vivo*; MAO inhibitors should prevent oxidation of catecholamines and thereby prevent formation of opioids and consequently of ethanol (opioid) dependence which they do not. The formation of opioids from catecholamines during ethanol metabolism may have biological significance but it is doubtful that the reported increased turnover of brain catecholamines (Clouet and Ratner, 1970), or possibly serotonin (Way, Loh and Shen, 1968; not confirmed by Cheney, Goldstein, Algeri and Costa, 1971)

²Although Davis (1973) reports that the addition of phenobarbital to brain stem homogenates resulted in enhanced production of norepinephrine-derived tetrahydroisoquinoline alkaloids. The significance of this observation is not clear because phenobarbital is not metabolized in the brain, 30% being excreted unchanged through the kidneys and the rest is metabolized in the liver.

observed concomitant with the development of dependence on opium alkaloids, can be extrapolated to ethanol withdrawal reactions.

Brodie, Spector and Shore (1959) have suggested that in the central nervous system serotonin mediates the function of the "trophotropic system" (drowsiness, sleep, decreased psychomotor activity) and norepinephrine mediates the function of the "ergotrophic system" with essentially the opposite effects. A simplistic application of this hypothesis might lead one to expect an increase of serotonin or decrease of norepinephrine, or both, during chronic ethanol intoxication and perhaps the opposite during withdrawal. To date, no consistent picture has emerged from a large body of published data regarding the effects of ethanol on brain neurohumoral amine concentrations, turnover rates, metabolism, or release (Feldstein, 1971; Wallgren, 1971; Kuriyama, Rauscher and Sze, 1971; Palaic *et al.*, 1971). The possibility that acetaldehyde, rather than ethanol, mediates changes in neurotransmitter substances is under active investigation (Truitt and Walsh, 1971). The present controversies in this area are likely to be resolved with the development of newer sophisticated biochemical methods. But the effect of ethanol or acetaldehyde on *peripheral* biogenic amine metabolism (mostly in the liver, Eccleston *et al.*, 1969), as studied by blood and urine concentrations, is probably not pertinent to ethanol withdrawal because the blood-brain barrier prevents these amines from entering the brain in significant amounts.

Membranes

It is conceivable that ethanol, like chemically inert, systemic anesthetic agents (Pharmacology Society Symposium, 1968), has primary physicochemical effects on membranes, which in turn cause secondary metabolic alternations in cells including turnover of neurotransmitters. The postanesthesia emergence delirium (Eckenhoff, Kneale and Dripps, 1961) resembles clinically withdrawal states. The observation that the nonmetabolizable bromide ion may induce withdrawal signs (Freund, 1971) also suggests that perhaps the primary site of addictive drug action is at the membrane level.

The dissociation of calcium and magnesium ions from receptor sites in the membranes appears to initiate depolarization and thereby formation and conduction of action potentials. At present we do not know the structure of the molecules involved in calcium donation and acceptance and how such membranous calcium shifts result in configurational changes that in turn alter membrane pore permeability to sodium and potassium. Alcohols like isopropanol increase the binding of calcium and magnesium to nerve phospholipids and may thereby oppose depolarization (Ehrenpreis, 1965; Ehrenpreis and Teller, 1972). An ionic mechanism has also been proposed for the action of local anesthetics (Dettbarn, 1971) which may compete with calcium and other ions for membrane receptor sites thereby opposing depolarization. If chronic ethanol consumption leads to a sustained increase in calcium binding by membrane phospholipids as suggested by Ehrenpreis then it may be plausible to postulate that the acute reversal of this alcohol induced calcium binding is the basis of the CNS hyperirritability during withdrawal. If this were the case, then local anesthetics may be able to block these effects of calcium release after cessation of ethanol consumption by competing with the released calcium for membranous receptor sites, including calcium or magnesium activated enzymes. This possibility is supported by the demonstration that Lidocaine, a local anesthetic, in non-sedative doses prevents withdrawal seizures in mice (Freund, 1973). It is therefore conceivable that the primary effect of ethanol is at the membrane level of biological organization, initiating a series of biochemical events that express themselves as physiological

dependence at the clinical level. The current knowledge of the membrane effects of ethanol has been extensively reviewed by Kalant (1971). It is unfortunate that in many *in vitro* systems ethanol effects are demonstrable only with ethanol concentrations that are considerably above the lethal limits for man (approximately 0.12 Moles in blood). As ethanol rapidly traverses all biological membranes and equilibrates with the water space of the system, this criticism is more cogent than with other drugs.

Tolerance

In opiate addiction the development of tolerance is prominent: increasing amounts of a drug are necessary to induce a biological effect and the lethal drug dose may increase hundred-fold (Fraser, 1957). The lethal dose of ethanol, however, does not appear to be increased significantly in man or animals after prolonged ethanol consumption. But with more subtle behavioral measures functional tolerance is demonstrable with a wide variety of drugs including ethanol as reviewed by Kalant, LeBlanc and Gibbins (1971).

As Seevers and Deneau (1963) have pointed out, the development of dependence and tolerance are concurrent but not necessarily interdependent. Alternatively, Kalant, LeBlanc and Gibbins (1971) conclude from their extensive review of the literature of tolerance to non-opiate drugs that the development of acute (intrasessional) tolerance, chronic tolerance and severity of withdrawal reaction are on a quantitative continuum. Up to a certain maximum, the greater the continuous drug exposure in terms of blood concentration $\times$ time, modified by the behavioral state of the animal and previous drug exposure, the greater is the expected adaptive tolerance or the severity of the withdrawal reaction. The parallel development in time of the degree of tolerance and the severity of withdrawal reaction on continued and on repeated drug administration is compatible with this concept (Kalant, LeBlanc and Gibbins, 1971).

Chronic ethanol consumption may result in a relatively modest increase of the rate of ethanol metabolism (Mendelson, 1968). Metabolic or dispositional as opposed to functional, cellular (or "tissue") tolerance probably plays no direct role in the development of dependence on ethanol (Kalant, LeBlanc and Gibbins, 1971).

CONCLUSIONS

The preceding discussion makes it evident that animal models of withdrawal syndromes are destined to play an important role in the elucidation of the pathogenesis of physiological dependence and ultimately in the development of improved therapy and prophylaxis for man. Each of the several models available has inherent advantages and limitations regarding practicability, expense, potential pharmacological relevance to man, potential for applying behavioral, genetic, electrophysiological or biochemical methods to the model and the time required to obtain the desired information. The final test of the usefulness of the model is whether it yields information or concepts applicable to the disease in man.

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Are Opiate Tolerance and Dependence Reversible? Implications for the Treatment of Heroin Addiction

Avram Goldstein¹

INTRODUCTION

“One fix of heroin and you’re hooked for life.” “I can take it or leave it without getting hooked, and I know lots of friends who’ve been chipping for years.”

“Once an addict, always an addict.” “The only real solution is to live drug-free, and anyone who really wants to can do it.”

In these pseudoquotations are summed up the extremes of opinion about the issues I shall discuss here. The first pair of contrasting positions reflects a controversy about the etiology of opiate dependence, the time courses of its onset and decay, the factors that determine the degree of dependence, and the reversibility of the process. This question is subject to laboratory as well as clinical study. The second pair of positions reflects a deeper and more fundamental controversy about the nature of drug dependence in addicts. Adequate experimental tools for resolving this issue conclusively do not appear to be available yet.

EMPIRICAL AND THEORETICAL ISSUES

Steady-state Theories of Tolerance and Dependence

The biochemical changes in brain that underlie and are responsible for the state of drug dependence have not yet been identified. Virtually every known neurotransmitter has

¹Addiction Research Foundation and Stanford University, Palo Alto, California, 94304.

been implicated, either in the acute actions of the opiates or in the tolerant-dependent state (Dole, 1970). One of these may indeed be primarily involved, with consequent secondary changes in the content or turnover of the others; or all the reported changes may be secondary to some as yet unknown primary effect. Without knowing what substance or process is responsible, we may nevertheless study some factors that influence the tolerant-dependent state.

An explicit model for biochemical change was proposed by D. B. Goldstein in 1961 (Goldstein and Goldstein, 1961), and expanded upon later (Goldstein and Goldstein, 1968). She suggested that if a drug inhibited an enzyme that was repressible by its own product, and if that product were essential for brain function, the inevitable result would be the state we call dependence. If the product, for example, were a neurotransmitter, the drug would reduce its availability at synapses, and the primary drug action would correspond to a deficit of that neurotransmitter. This, in turn, would lead to derepression of the enzyme, causing increased enzyme synthesis, an increase in the steady state level of enzyme, and a restoration of the normal neurotransmitter supply, despite the continued presence of the drug. Tolerance and dependence would result — tolerance, because the drug effect would have been overcome, and more drug than usual would be required to elicit the drug action again; dependence, because removing the drug would unmask an abnormal underlying state, the excessive amount of disinhibited enzyme leading to abnormally increased neurotransmitter availability, with physiologic disturbances opposite to those caused by the drug in the first place. Two time courses were predictable: a rapid acute drug effect, followed by a much slower adaptation to the presence of the drug, at a rate corresponding to the turnover rate of the enzyme; then, on withdrawal, a rapid onset of withdrawal symptoms, as fast as the drug disappeared from the system, followed again by a slower process, the return of enzyme levels to normal, accompanied by loss of tolerance and dependence.

The essential feature of this theory was not its focus upon an enzyme required for neurotransmitter synthesis — any other essential protein would fit equally well. The central points, which had not previously been formulated, were these: (1) the target protein upon which the drug acts undergoes a steady state shift (e.g., an increase in its steady state level) as a consequence of its interaction with the drug; (2) the change in steady state level of drug receptor has the effect of opposing the drug action, thus making it necessary to raise the drug concentration (dose) in order to produce drug effects (i.e., tolerance), and producing a state of apparent normality in which the drug is present and its effects are overcome (i.e., dependence), so that withdrawal of the drug allows the countervailing mechanisms to become manifest and produce symptoms and signs of abstinence.

With respect to the opiates, no one knows yet if any relevant protein pool expands in the postulated manner during the tolerant-dependent state, nor if the protein (if any) that does expand is the same as that upon which the drug acts. Collier (1966) later proposed that what may expand is a pool of postsynaptic receptors, possibly not the same receptors upon which the opiates act. He suggested that serotonin receptors might become sensitized as a result of exposure to morphine, and that supersensitivity to serotonin might be related to tolerance and dependence. Experimental evidence from my laboratory lends support to this serotonin supersensitivity theory (Schulz and Goldstein, 1973).

Evidence of Time Course and Reversibility in Animal Experiments

Whatever protein is altered, in its synthesis or degradation, as a consequence of exposure to opiates — whichever of the theories may be correct — it is implicit in all of them that the tolerant-dependent state is a reversible one. We tested this in a series of experiments in mice to quantitate tolerance and dependence as well as possible, and to establish the time courses of these phenomena. We studied the locomotor activity caused by opiates in this species, which could be measured readily in photoelectric activity cages. Because of a high degree of variability between animals, we used each mouse as its own control, referring the running activity caused by later doses to that produced by the first injection of the opiate levorphanol. We chose a fixed dose: the moderate dose that just produces maximum locomotor activity and analgesia in the nontolerant animal. The question is: what is the effect upon tolerance if we vary the interval between doses, keeping the dose constant? The reason we asked this question is that, in the case of humans, we have little control over the dosage. If the dose is too small, no effect will be obtained, and the experiment becomes pointless. If the dose is too large, the overdose range will be encountered. Just as addicts try to use a dose of heroin sufficient to be euphorogenic but not dangerously large, we chose the dose by the same criteria in mice. The experiments then consisted in injecting (i.p.) 20 mg/kg of levorphanol at perfectly regular intervals, around the clock, and measuring all the locomotor activity produced by each dose.

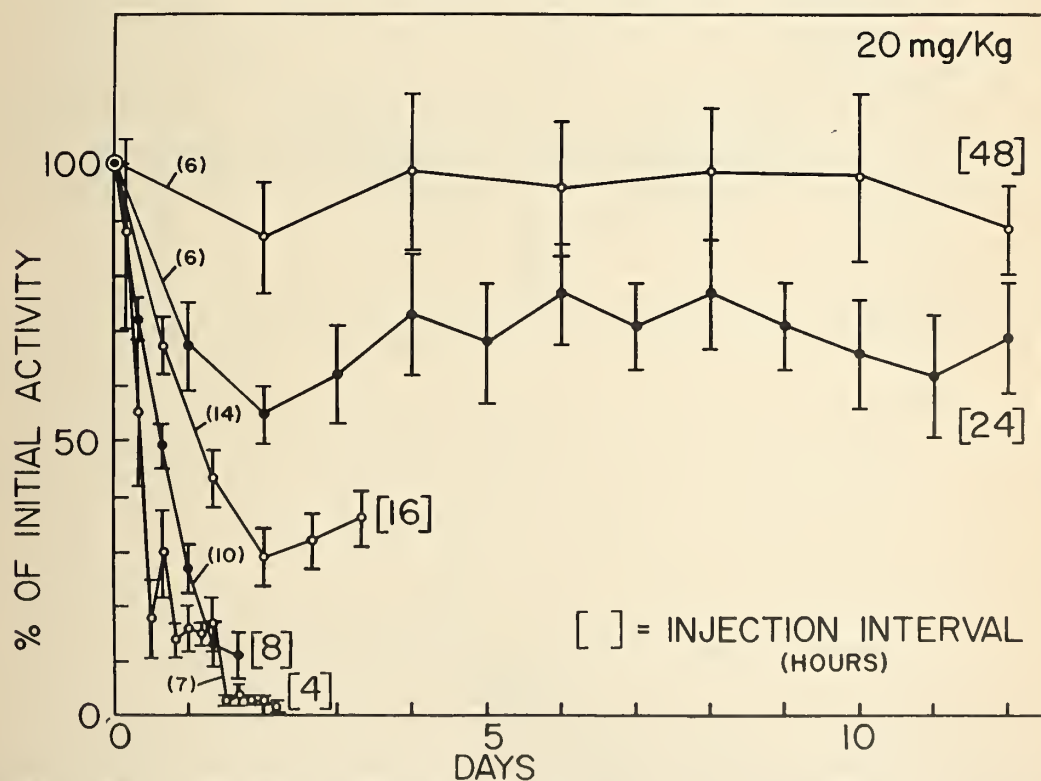


Figure 1: *Effect of different injection intervals upon the development of tolerance to levorphanol. Mice were housed three to a cage (one to a cage for the four-hour interval). Number of cages is indicated in parentheses. Total running activity between injections was expressed as percentage of the initial value for each cage. Interval between injections is shown in brackets to right of each curve. Each point is a mean value; $\pm$ S.E. is shown in the customary way. The single dose was constant: 20 mg/kg of levorphanol.*

The results of these experiments (Goldstein and Sheehan, 1969) are summarized in Fig. 1. All our findings were compatible with the steady-state theory. It appeared that each dose produced some quantum of the biochemical change responsible for tolerance, and that this change had its own time constant of decay, independent of the biologic half-life of the drug (less than one hour). At intervals of 48 hours, the injections never produced any tolerance, regardless of how long they were continued; thus, 48 hours were sufficient for complete reversal of the effect of a single dose. At 24 hours, there was a slight residue of the tolerance induced by the previous injection so slight that the steady state resulting from injections at this interval represented only a small degree of tolerance. At intervals shorter than 24 hours, the buildup of tolerance was considerable; the rate of development of tolerance, as well as the ultimate steady state level of tolerance, were functions of the interval in the range 8-24 hours. When the interval was shorter than 8 hours, no more rapid development of tolerance could be achieved, as though we had reached the intrinsic rate at which the underlying process could respond (e.g., the turn-

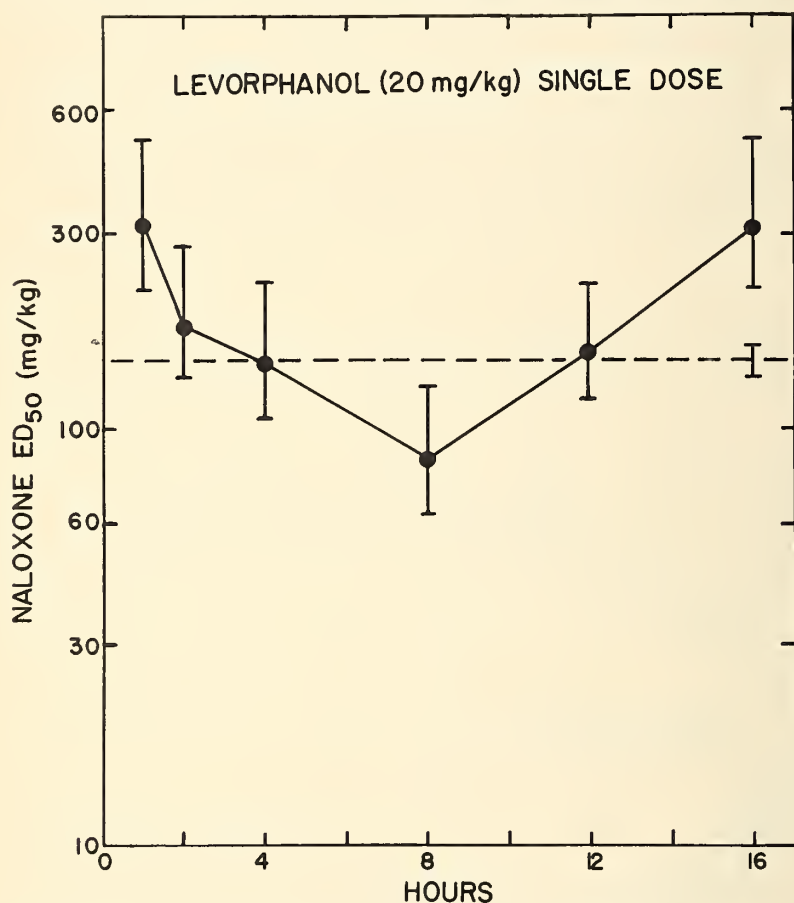


Figure 2A: Initiation of physical dependence by a single dose of levorphanol. At zero time mice were given a single 20 mg/kg levorphanol injection intraperitoneally. Groups were then tested with several doses of naloxone at various times thereafter to determine the ED₅₀ for precipitated jumping. The dashed line indicates the ED₅₀ for naloxone-induced convulsions in control mice. Each ED₅₀ value above the dashed line is an extrapolation from the lower dose segment of a quantal log dose-response curve obtained at the given time. Standard errors of the ED₅₀ estimates are shown by brackets above and below each data point. Each point is based on 45 animals.

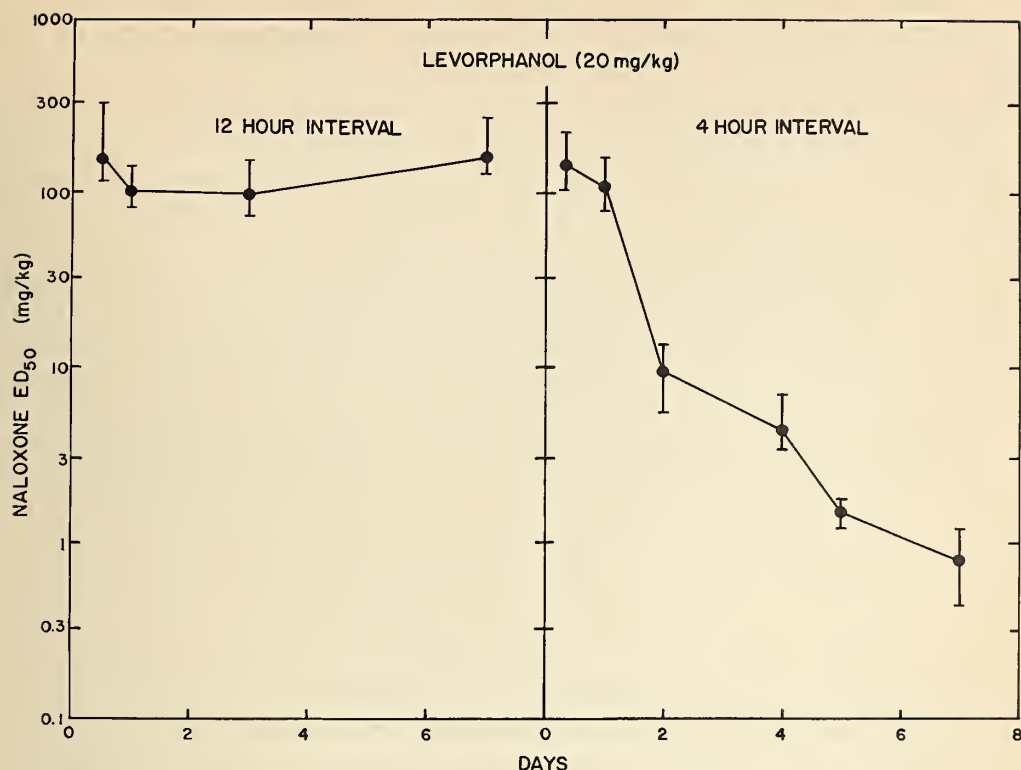


Figure 2B: *Development of physical dependence on 12-hour and 4-hour schedules of levorphanol injections (20 mg/kg). Groups were tested with several concentrations of naloxone 12 hours or 4 hours, respectively, after the previous injection of levorphanol in order to determine the ED₅₀ values for naloxone-induced jumping. Symbols as on Figure 2A.*

over rate of the critical protein). On discontinuing drug injections, tolerance disappeared completely in 24 hours. Repeated cycles of drug administration produced results indistinguishable from the first.

There was no easy way to test the hypothesis that a single drug injection caused a small amount of tolerance, because the presence of an opiate in the animal complicates the testing. This could be studied, however, with respect to dependence. The use of the antagonist naloxone to precipitate the withdrawal syndrome greatly simplifies the quantitation of the degree of dependence, and this action of the antagonist is not affected by the simultaneous presence of an opiate agonist. Normal mice never display jumping behavior, and naloxone in normal mice never elicits jumping even up to lethal doses (death is due to convulsions). Opiate-dependent mice jump off a platform after administration of naloxone (Way, Loh, and Shen, 1969), and their sensitivity to naloxone reflects the extent of their exposure to an opiate, and thus, obviously, the degree of their dependence. The more dependent, the more sensitive are they to naloxone. We administered the same moderate (20 mg/kg) dose of levorphanol as in the tolerance experiments, then tested large groups of animals at different subsequent times, by giving various doses of naloxone, thus determining the naloxone ED₅₀ and its standard error (Cheney and Goldstein, 1971). The results were very clear, as Fig. 2 shows. Naloxone jumping was evident a few hours after the levorphanol injection. The degree of dependence increased for a number of hours, then waned, disappearing after about 16 hours. This result allowed

us to predict the effects of various interval schedules. For example, an injection of the opiate every 24 hours caused only very little more dependence than had the single dose. As with tolerance, the dependence caused by a previous dose was virtually gone 24 hours later, so no cumulative dependence occurred. On the other hand, opiate injections at 4-hour intervals led to a very marked cumulative dependence, with sensitivity to naloxone at least two orders of magnitude greater at the steady state than with the 24-hour interval.

In our experiments, both with tolerance and with dependence, the phenomena were (as required by the theory) completely reversible in about 24 hours. Moreover, no persistent effects whatsoever were seen; subsequent cycles of tolerance-dependence followed exactly the same time course, for a given interval schedule, as the original one. We cannot reconcile our findings with certain conflicting data reported by others. A partially irreversible tolerance to certain morphine effects in rats has been reported (Cochin and Kornetsky, 1964). Persistence of opiate preference was seen in rats (Wikler and Pescor, 1970; Wikler, Pescor, Miller and Norell, 1971) about a year after the last exposure to an opiate. Apparent withdrawal signs could be evoked in monkeys months after withdrawal of morphine (Goldberg and Schuster, 1970), but these important findings, based on only a few animals, have not been confirmed. In human post-addicts Martin and Jasinski (1969) found slight but definite physiologic abnormalities (not characteristic withdrawal signs) many months after withdrawal, but no concurrent control group was used in this study. It seems possible that the small deviations observed in blood pressure, pulse rate, body temperature, and pupillary diameter, could have resulted from seasonal or other temporal variables. It is not surprising that state-dependent learning could simulate persistent tolerance, or that conditioning effects should persist for a very long time. What needs to be explored more deeply and confirmed are those findings of persistent tolerance or dependence in which objective physiologic effects were quantitated and in which psychologic factors were adequately controlled.

The Critical Interval in Humans

The concepts outlined here were examined in discussions with heroin addicts, to see if the same principles were likely to apply as in mice. Addicts at admission to a methadone program were questioned as to their own experiences concerning intervals between heroin injections in relation to the development of tolerance and dependence, i.e. "getting a habit". Occasional use is referred to as "chipping"; regular daily use is a "run". The predominant view was that "chipping" could probably be sustained on an indefinite basis, without leading to a "run". However, few could cite concrete instances of friends who continued occasional use for many months or years. There was good agreement that the danger of developing a habit ("getting strung out" and having to increase the dose, and becoming sick without the drug) increased sharply as the frequency of use increased to more than a few times weekly. Thus, it appeared that the critical interval in man might not be too different from that in the mouse, about two days. Daily use was recognized by all as leading inexorably to tolerance and dependence, and thus, to even greater frequency of use, to compensate for the shortened duration of action in the tolerant state.

These observations raise an interesting point. Heroin addicts are certainly knowledgeable about these matters, and they display a good understanding of the critical interval. Yet, if "chipping" for very long periods of time exists at all, it appears to be rare.

Why is it difficult for the addict to maintain a sufficient interval between heroin injections, and thereby to make his use of heroin optional and recreational rather than compulsive? The advantages to him, given the present legal status of heroin and its inflated black market price, would be considerable. Perhaps the single-dose dependence experiments suggest an answer. Possibly subtle withdrawal effects, not readily apparent as physical signs, produce a craving for more heroin at some time after each single dose. The net effect could be an insidious shortening of the interval. The primary reinforcement from the first dose would be supplemented by an additional source of reinforcement at subsequent doses due to relief of the subclinical withdrawal phenomena. A practical possibility for counselling might be to motivate attempts to keep the interval long enough and gradually to increase it, rather than to attempt complete abstinence all at once. Although not an optimal solution, the continued use of heroin on an occasional, optional, basis would surely be preferable to the typical cycle of abstinence and relapse culminating in a catastrophic "run".

Irreversibility and "Metabolic Disease"

The question of reversibility is not trivial, it is central to the entire issue of how we should treat and rehabilitate opiate addicts. In its most explicit form, the irreversibility thesis has been stated by Dole and Nyswander (1967) as the "metabolic disease" theory. According to this theory, the use of opiates provokes some irreversible biochemical change which, however, can be remedied by administration of opiates. I shall examine the evidence for and against this theory, but first I would like to consider whether or not it is plausible in terms of our present knowledge. How could use of a drug create a pathologic state the cure for which is that very drug? Are there examples of such mechanisms? I think there are. In a feedback loop, if the limits of regulation are exceeded, permanent damage could result. Suppose increasing doses of cortisol are administered continuously over a very long time. Endogenous corticotropin secretion will be inhibited completely, and consequently, adrenal cortical tissue will atrophy. A state can result, in which dependence upon the exogenous cortisol has been produced; an adrenal crisis (withdrawal syndrome) will ensue if it is stopped abruptly. Necessary for such a mechanism is the endogenous production, under feedback regulation, of a substance similar or identical to the exogenous drugs.

Can we imagine that an endogenous opiate acts as a neurotransmitter at certain synapses? It is all too easy to spin such a yarn. *First* one can invoke natural selection for the teleologic reasonableness of an opiate neurotransmitter to modulate various stimuli. Acute pain, we can argue, is useful and has survival value. But is there not need for a means of turning off chronic pain, which can only impede the efficiency of escape or fighting behavior and degrade the intelligent control of behavior? *Second*, one can cite experimental evidence suggestive of the endogenous synthesis of opiate molecules. The initial steps in morphine synthesis in the opium poppy are all present in mammalian liver and brain: the condensation of dopamine with dopamine aldehyde, and the eventual production of tetrahydropapaveroline, a direct precursor of morphine (Holtz, Stock and Westermann, 1963, 1964; Kirby, 1967; Davis and Walsh, 1970). This and other isoquinoline alkaloids have certain pharmacologic actions. But they do not have morphine-like effects, and their further transformation to a morphine-like molecule in animals has not been demonstrated. *Third*, the remarkable experiments of Mayer, Wollfe, Akil, Carder and

Liebeskind (1971) and of Mayer, Akil and Liebeskind (1973) indicate that naloxone, which in general has no positive actions except in opiate dependent organisms, antagonizes analgesia produced by electrical stimulation in the brain stem region surrounding the aqueduct and fourth ventricle in rats and cats, a region shown to be a site of the analgesic action of morphine (Vigouret, Teschemacher, Albus and Herz, 1973). Alternative explanations are, obviously, possible, but it could be imagined that electrical stimulation here acts by releasing an endogenous opiate neurotransmitter to act upon postsynaptic opiate receptors, and that these are blocked by naloxone. We have made unsuccessful attempts to detect opiates in normal mouse brain by means of an immunoassay technique (Schneider, Lindquist, Wong, Rubenstein, and Ullman, 1973), but the assay sensitivity required that more than 16 pmoles per brain be present.

Suppose an endogenous opiate neurotransmitter were present in "morphinergic" neurons. Administration of an exogenous opiate would probably shut off its synthesis, through operation of the known transsynaptic regulatory mechanisms (Weiner, 1970; Glowinski, Hamon and Hery, 1973). Conceivably, after prolonged shutdown, as with adrenal cortical cells, the specific neurons might continue to synthesize or release the endogenous opiate defectively. A mechanism like that whereby 6-hydroxydopamine (Thoenen and Tranzer, 1968) or 5, 6-dihydroxytryptamine (Baumgarten, Bjorklund, Lachenmayer, Nobin and Stenevi, 1971) destroys specific neurons, might also play a role. Then, clearly, with respect to those neural systems in which the endogenous opiate acted, the cycle of addiction would have a permanent (or at least, long persistent) aftermath. In this version, it should be noted, tolerance and dependence would develop as a result of shutdown of endogenous opiate synthesis, and the time course would be determined by the turnover of the rate limiting enzyme in the biosynthetic pathway.

Such speculation as the above is not to be taken too seriously unless substantial supporting evidence is adduced, but it serves a useful purpose in showing how a metabolic disease might conceivably be engendered through opiate use.

The concept of "metabolic disease" apparently was inspired by the well-known high relapse rate among heroin addicts after voluntary or forced detoxification. It became a major justification for methadone maintenance. And the unquestioned success of methadone programs seemed to confirm the notion that ex-addicts "need" an opiate in order to function. What they need methadone for was never precisely defined. I have discussed this question at length elsewhere (Goldstein, 1972). What they need a *program* for is clear enough, especially if that program provides job placement and other rehabilitative services. Obviously, during the dependent state there is truly a metabolic disease that is remedied by opiates. That is a trivial statement. The question is what happens after withdrawal is complete. Is there then a residual, persistent need for an opiate? And if so, how is it manifested? It was postulated that a "narcotic drug hunger" persisted, but no criteria for detecting and measuring this phenomenon have been advanced. Apparently, "narcotic drug hunger" is that state of affairs which leads to relapse, to the renewed use of heroin after a period of abstinence. The prevention of relapse is the central challenge in the treatment of heroin addiction. Were it not for the relapse phenomenon, we could eliminate the heroin problem in a few weeks by detoxifying all the addicts. What, then, is the nature of the "narcotic drug hunger" that drives abstinent ex-addicts to using heroin again? My limited observations on a few hundred addicts indicate that it is a periodic rather than a constant phenomenon, and that it is very often triggered by external stressful circumstances or by contact with situations or people evocative of previous "hustling" or "fixing" activities. Thus, most relapses are probably explained sufficiently

well by Wikler's "conditioned withdrawal" hypothesis (Wikler, 1971).

One could argue, however, that the underlying metabolic defect is not continuously manifest but only predisposes the ex-addict to episodes of irrational compulsive drug-seeking behavior that no normal person, knowing all the consequences, would indulge in (Dole, 1972). This position does not even require that the metabolic defect be caused by opiate use; it could be a preexisting neurochemical disorder that is normalized by opiates, i.e., a subtle genetic defect of brain function. Hypothetical mechanisms can be proposed. For example, we know that in brain (Beleslin and Polak, 1965) as in the myenteric plexus controlling peristalsis (Paton, 1957; Cox and Weinstock, 1966), opiates interfere with the release of acetylcholine from cholinergic neurons. It follows that a biochemical defect resulting in excessive acetylcholine release or insufficient acetylcholine hydrolysis could produce a variety of disturbances of psychologic function, which would be normalized by opiates. According to this view, people thus afflicted would be likely to become opiate addicts if given the opportunity to try an opiate. They would feel and function better after heroin than before, and might therefore be inclined to seek it out again. Others would not wish to repeat the opiate experience because it would have dysphoric rather than euphoric effects upon them. Findings by sociologists (Chein, Gerard, Lee, Rosenfeld and Wilner, 1964; Robins and Murphy, 1967) tend to support this position, in that most adolescents who try heroin do not become addicts. On the other hand, the fact that *all* monkeys learn to take heroin by self-injection shows that in that species heroin is a primary reinforcer, requiring no preexisting defect for its "rewarding" actions to occur. We showed some years ago that even with a licit drug like caffeine, people differed greatly in their responses, according to their use of the drug (Goldstein, Kaizer, and Whitby, 1969). In double-blind placebo-controlled experiments we found that heavy users of caffeine experienced euphoric effects, whereas nonusers experienced dysphoria. We could not discover if these differences were consequences of prolonged chronic exposure or lack of exposure to the drug, or whether they preexisted and thus helped to determine the use patterns. It would not be impossible to conduct a prospective study of this question with such a mild stimulant as caffeine, and thus possibly to document the proposition that genetic predisposition to drug abuse might exist. Genetic traits influencing opiate intake in free-choice experiments in animals are known (Eriksson and Kiianmaa, 1971; Nichols and Hsiao, 1967). Thus far, however, no unique psychologic or physiologic abnormalities have been detected in ex-addicts as compared with appropriately matched non-addict controls.

Evidence against a "metabolic disease" hypothesis — whether preexisting or caused by opiate exposure — comes from research on methadone maintenance. Every methadone program enjoys some successes and suffers some failures in assisting ex-addicts to remain abstinent from heroin. "Dirty rates" (i.e., the per cent of patients using illicit heroin during a given week or month) vary from a few per cent to over 50 per cent in different programs, despite the fact that methadone is administered in the same dosage range in all of them. I have seen the "dirty rate" change in the same program from 5 per cent to 60 per cent over a period of years, with changes in patient population, staff, program management, and other variables. These findings tend to show that methadone, although it is an opiate, does not by itself curb "narcotic drug hunger" or prevent heroin use. Our most striking finding was that when dosage was changed in a blind fashion from 80 mg daily to 160 mg daily in one group, from 80 mg to 40 mg in another, and held constant at 80 mg in a third, no differences in heroin use were observed (Goldstein and Judson, 1973). An essential feature of such experiments is that the dose changes be made very

slowly, so that tolerance keeps pace with the changing dose. It is very easy to stop heroin use by suddenly making a large increase in the methadone dose, i.e., by letting the patient "get loaded" on methadone. However, if the same large dose is repeated daily, tolerance develops, so that eventually the euphorigenic action is lost. Then the patient is very likely to use heroin again. Patients on doses of methadone up to 160 mg have continued using heroin, only to give it up later, after intensive counselling, and even though the dose was reduced to a much lower level. Thus, sufficient methadone must be given (at least 40 mg for most patients) to exceed some threshold, but there appears to be no dose-related relief of "narcotic drug hunger" above this threshold.

Does Methadone Have Agonistic Effects in Stabilized Patients?

In some instances, perhaps where the patients were not truly dependent on heroin, stabilization on a placebo rather than on methadone has been successful (Berry, 1972). But it has seemed likely (Blake and Distasio, 1973) that in most patients methadone does indeed have a pharmacologic effect in addition to maintaining the tolerant-dependent state. If methadone had no such agonistic effect, it would be possible to carry out a very slow blind withdrawal to complete abstinence without recognition by the patient. We have tried to do this during the past three years. Our consent form for slow withdrawal at the patient's request states that we will reduce the dosage at an unknown rate, guaranteeing only that the withdrawal will be complete at the end of six months. We have found, in agreement with the experience of others, that regardless of the rate of dose reduction (even 10% per week or less) and regardless of the initial maintenance level (even 40-50 mg or lower), a dose is reached with most patients at which compulsive heroin-seeking behaviour appears. This may happen even in patients who have taken no heroin for a year or more. Catastrophic stressful events also suddenly intrude into the patient's life, although they had not been evident at higher doses, making one wonder if they were evoked by changes in the patient's behavior.

The assumption that patients maintained for long periods on methadone become completely tolerant to the agonistic opiate effects requires careful reexamination. It is well established that tolerance to different effects develops at widely varying rates. Thus, constipation persists for months, diminishing gradually and finally disappearing in most patients. Drowsiness, often seen during the induction phase, usually subsides in a matter of weeks. Is it possible that subtle effects on brain function persist as long as the drug is administered at a sufficient fixed dose, without development of tolerance? Is it possible, in other words, that methadone acts on many patients as a psychotropic agent, like the phenothiazines or tricyclic antidepressants, and that the cross-tolerance ("blockade") and sustaining of an opiate-dependent state are secondary or even irrelevant? This is difficult to test. No pre-methadone drug-free baseline can be obtained, because the patient is using heroin before he enters the methadone program; thus, even before-and-after symptom surveys, such as we have routinely conducted (Goldstein, 1972; Garbutt and Goldstein, 1972; Goldstein and Judson, 1973), cannot be interpreted with reference to a "normal" state of the given patient.

Our symptom survey data for patients stabilized at 80 mg daily for six months revealed a great many persistent complaints (Goldstein and Judson, 1973). Some of these, such as sweating and constipation, were present in more than half the patients, and complaints rated severe were voiced by as many as 15-20 per cent of patients in some

instances. Again, the problem in interpreting these results is that we do not know how these same patients would respond had they never used heroin and never received methadone. Insomnia, or complaints about sexual potency, for example, are quite common in the general population. Further light may be shed on this question by an experiment currently in progress, in which we conduct the symptom survey on matched pairs of methadone patients and individuals without drug histories. Before-and-after comparisons are absolutely essential in evaluating changes in the individual patient maintained on methadone as compared with his previous status while using heroin. Employing this technique, we found that during the first full year on methadone, contrary to certain dogmas, there was no increase in the excessive use of alcohol or amphetamines, and there was a significant decrease in use of illicit barbiturates. This belies the notion that addicts necessarily must "get high" on something, and that if heroin use is abandoned or substantially diminished, they will compensate by abusing other drugs. On the contrary, the data are what one would expect in a group of people who make a significant change in their lifestyles, reducing or abandoning heroin use, and concomitantly reducing contact with all drugs of abuse.

Withdrawal from Methadone

Implicit in the "metabolic disease" hypothesis is a prediction: that patients who do well maintained on methadone should fail after withdrawal from methadone, and should also not succeed if maintained on a narcotic antagonist. The latter prediction has not yet been sufficiently well investigated; it is of key importance for verifying or falsifying the hypothesis. Withdrawal, on the other hand, has been carried out in most methadone programs — against staff advice in programs dominated by the "metabolic disease" hypothesis, with staff encouragement elsewhere. I can report in a preliminary way on a planned withdrawal trial for which long-term followup is continuing. We believed that if withdrawal were to succeed, it would require a great deal of continuous supportive peer and counsellor interaction. The experiment was planned accordingly. Volunteers were solicited from about 500 active patients in a County methadone program. It was required that participants have been maintained on methadone for at least one year; that no use of heroin, barbiturates, or amphetamines have occurred during the previous six months; and that assessment by staff would rate the chances for success as good, based upon stability of employment, family relationships, and motivation. Forty participants were chosen. Counsellors specially selected and trained for this project were assigned about 10 patients each. A special evening clinic housed the program; patients attended twice weekly, participating in group sessions on those nights. All participants had been maintained on 50 mg daily or less. The withdrawal period was set at four months, with patients regulating their own rate of dosage decrease (dosage was open), limited only by the following inflexible rules: (1) that day by day the dosage must stay the same or be reduced but never be increased; and (2) that methadone dispensing would cease at the end of a four-month period. Breach of these rules removed the patient from the withdrawal project and returned him at once to the regular maintenance program. Twenty-one of the initial 40 successfully withdrew from methadone; the remainder experienced severe discomfort, felt "sick", often used heroin, in some instances underwent dramatic personality change (paranoia, depression, overt hostility, violent aggressive tendencies), and were therefore returned to the main program and restabilized on methadone. Of the 21 patients who

withdrew from methadone, 6 had used heroin at least once during the withdrawal period. A few actually switched from methadone maintenance to regular heroin use, then discontinued heroin successfully and have remained abstinent until now, four months later. Seven patients could be rated complete successes four months after discontinuance of methadone. They were abstinent from all illicit drugs, remained in close and frequent contact with a counsellor, and were leading well-organized and productive lives. Four others were in a good functional state but were using heroin at rare intervals, so their future is doubtful. Nine had relapsed to regular heroin use; 7 of these had returned to methadone maintenance, 1 was in jail, 1 was in hospital.

It would be very useful to be able to measure the degree of opiate dependence in man with greater refinement. The scoring techniques based on the original Himmelsbach procedure (Kolb and Himmelsbach, 1937) at Lexington are complicated, require a long time, and place very heavy stress on the most flagrant physical signs such as fever, vomiting, and gooseflesh. What may bother patients as much or more are mental and emotional disturbances such as depression, insomnia, and irritability. A peculiar paradox is seen in withdrawal from methadone. Data from Lexington showed clearly that methadone withdrawal was much milder than morphine withdrawal, although lasting a great deal longer (Isbell, Wikler, Eddy, Wilson and Moran, 1947). However, patients withdrawing from methadone tell us insistently that it is much worse than withdrawal from heroin. What they mean, questioning reveals, is that a peculiar dysphoric state lasts many weeks — a seemingly unbearably long time — although they readily concur that the physical symptoms are quite tolerable.

Long-term followup is obviously essential in evaluating methadone withdrawal. At the present time the outcome could be considered partial success or partial failure, depending upon one's bias. It is true that 82 per cent of a highly selected group could not withdraw from methadone and remain abstinent, despite the provision of favorable circumstances and an intensive counselling relationship that would be hard to justify on economic grounds for very large numbers of addicts. On the other hand, it is also true that 7 of 40 patients were able to withdraw successfully and remain abstinent after long-term maintenance on methadone. This seems to indicate that at least in some of the addict group, carefully planned reversal of the methadone dependence can be achieved, and that in such cases no "metabolic disease" manifests itself. This result is also consonant with the fact that considerable numbers of ex-addicts have become abstinent through a wide variety of drug-free rehabilitation programs, and continue to function in an abstinent state.

CONCLUSIONS

A key issue in understanding the basis of dependence on opiate narcotics and formulating successful treatments for heroin addicts concerns the reversibility of the underlying disorder. If there is a preexisting (genetic) defect of biochemical function in the brain, or if opiate dependence itself induces an irreversible defect, and if such a defect is compensated by opiates, it follows that opiate maintenance is the indicated treatment. If the "metabolic disease" hypothesis could be proved or disproved, the present raging controversies (based upon philosophic convictions rather than scientific analyses) about how to deal with narcotic addicts would subside.

I have summarized evidence from animal experiments and from research in metha-

done maintenance programs, which seem to bear upon this issue. No conclusive answers have yet emerged. Biochemical answers will only be obtained when we learn in detail how the interaction of a narcotic opiate with its specific receptors in neurons triggers the chain of events that result in the acute agonistic effects and that eventually lead to the tolerant-dependent state. Research with addicts needs to be focused much more sharply than hitherto upon the questions that need to be answered if the issue of reversibility is to be resolved.

Describing opiate addiction as "drug dependence of morphine type" probably served a certain clarifying purpose when it was first adopted by the World Health Organization (Eddy, Halbach, Isbell and Seevers, 1965). It is nevertheless deficient in some important ways. The old word "addiction" focused attention on the life style and functional status of the individual in relation to society, which is really much more important than whether or not a drug is ingested on a regular schedule. The point is of more than semantic importance. If the addict's problem is *defined* as drug dependence, it follows automatically that opiate maintenance can not be considered a valid treatment. If the "metabolic disease" concept were even partly correct, however, methadone maintenance would have to be viewed as medical treatment. Any patient whose physical or mental function is abnormal unless he takes medication regularly is "dependent" on that medication. This would seem to be just as true for patients ingesting a daily dose of methadone as for those stabilized on diphenylhydantoin, tricyclic antidepressants, phenothiazines, or even cardiac glycosides.

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Historical Antecedents as Determinants of Tolerance to and Dependence upon Psychoactive Drugs

A. E. LeBlanc¹ and Howard D. Cappel

INTRODUCTION

Drug self-administration at a level that produces tolerance and dependence is characterized in the real world by its episodic nature. The alternation of periods of abstinence and drug use may be produced by spontaneous choice, legal or medical intervention, or economic factors. Despite the intermittent occurrence of drug-free intervals, sometimes of considerable duration, there have been many anecdotal reports that users are not "normal" when re-exposed to the drug in the sense that they acquire a different response to the drug than people who have not been so exposed.

For example, there have been suggestions in humans and animals that there is a protracted abstinence pattern. The bulk of the evidence comes from work with opiates (Himmelsbach 1941; Martin, Wikler, Eades, and Pescor 1963; Wikler and Pescor 1967; Goldberg and Schuster 1969), although Oswald (Oswald and Thacore 1963; Oswald 1968) has demonstrated a similar phenomenon with amphetamines and sedatives in man. It should be noted that in all of these studies, relatively sophisticated measurements were required to detect the persistence of the drug-induced changes.

In contrast to the previous studies, it has frequently been shown that during periods of abstinence, there is a return to normalcy. A number of studies with animals have shown that after a period of recovery, the response to alcohol, opiates and amphetamines returns to baseline levels (Goldstein and Sheehan 1969; Kalant, Le Blanc and Gibbins 1971a).

¹Addiction Research Foundation, 33 Russell Street, Toronto, Ont., Canada M5S 2S1.

Additionally, clinical studies in man indicate a similar pattern; abstinence signs also disappear with days or weeks of cessation of treatment (Oswald and Thacore 1963; Oswald 1968; Kalant *et al.*, 1971a).

In summary, there is evidence in support of two apparently conflicting generalizations about the effect of prior drug history on subsequent response following a period of abstinence. It is possible to describe a number of ways in which the consequences of previous experiences of tolerance and dependence² might become manifest (or fail to do so) during subsequent drug exposure.

MODEL I: PROTRACTED TOLERANCE AND DEPENDENCE

A level of tolerance or dependence once attained may return to baseline very slowly during a period of abstinence. Should an additional cycle of drug exposure intervene before recovery is complete, tolerance and dependence would then build upon residual levels. This is a widely accepted idea when short intervals are involved; the disagreement is over the time required for complete recovery to occur. Clearly, Model I assumes a recovery period of considerable length.

MODEL II: INDEPENDENCE OF TOLERANCE AND DEPENDENCE EPISODES

Tolerance and dependence may disappear completely within a period of abstinence, leaving no effect on the subsequent development of tolerance and dependence. In this view, each episode, provided an adequate but short period of abstinence intervenes, is completely independent.

MODEL III: INTERDEPENDENCE OF TOLERANCE AND DEPENDENCE CYCLES

Tolerance and dependence may not be detectable in the time period of abstinence, yet still have an effect on the subsequent development of tolerance and dependence. This effect may take at least three forms: (i) the *rate* at which tolerance and dependence are re-elicited may be increased; (ii) the maximum attainable *level* of tolerance and dependence may be increased; (iii) both the rate and the maximum attainable level may be increased. This model assumes some relatively durable change in the organism resulting from a period of drug exposure, even though there may be recovery to baseline levels during a period of abstinence. Schematic representation of these three models is given in Figure 1.

EMPIRICAL EVALUATION OF THE MODELS

Model I

This model of tolerance and dependence is questionable because it requires a very extended period of recovery from prior exposure. However, there have been some data

²Although some features of tolerance and dependence seem to be linked (Kalant *et al.* 1971a) and others clearly not (Wallgren 1973), tolerance and dependence will be assumed to be linked inextricably for present purposes.

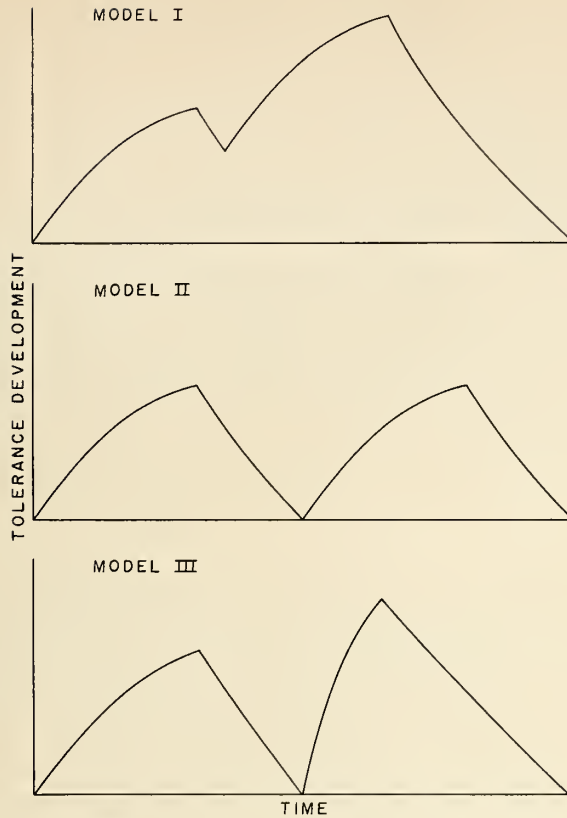


Figure 1 *Schematic representation of the three models of tolerance and dependence. See text for explanations. A similar description would apply to dependence.*

brought to bear on the issue that give it some credibility, at least for dependence.

Turning first to a consideration of tolerance, we find that few experimental studies have demonstrated protracted tolerance to drugs. However, this should not be surprising in view of the fact that so few researchers (Cox, Ginsburg and Willis 1973) have attempted to study the duration of tolerance. The dearth of information can be accounted for in several ways. The first is that tolerance is not viewed as pathological and has therefore not commanded the attention of as many workers as has dependence. The second derives from the problem that it is difficult to measure tolerance without affecting it. Hence, one is faced with methodological and conceptual problems of distinguishing residual tolerance from that produced by the test dose intended to measure the residual. Finally, the measurement of tolerance usually involves a great investment in testing procedures, especially in contrast to physical dependence, which can be assessed with relative ease.

In virtually all of the studies that have examined the issue, tolerance was reversible over a reasonably short time period (Goldstein and Sheehan 1969; Kalant *et al.*, 1971 a). The time for reversibility to occur must be longer than the typical intervals allowed between drug treatments in experiments on tolerance development, since tolerance is cumulative under such regimens. If one assumed that tolerance reversed completely between treatment doses in such experiments, its cumulative nature could only be explained by the interaction described in Model III, which is the only one that allows for a residual effect of treatment despite evidence of complete recovery between treatments.

There are two notable exceptions to the notion that the reversibility of tolerance is rapid (Cochin and Kornetsky 1964; Cox *et al.* 1973). The more famous of these is the demonstration by Cochin and Kornetsky (1964) that tolerance to morphine persisted for as long as a year. More recently, Cox and his co-workers (1973) determined the half-life of the reversibility of morphine tolerance to be nearly two weeks.

The evidence suggesting slow disappearance of dependence is more extensive, as several authors have described as protracted long term abstinence pattern. Goldberg and Schuster (1969) showed that naloxone could precipitate certain physiological disturbances months after morphine withdrawal in monkeys. Importantly, a control condition was included that tends to eliminate an explanation of the phenomenon in terms of conditioning (cf. A. Goldstein, this volume). Martin and his co-workers (1963) found that abnormalities similar to those of the acute withdrawal syndrome persist for months after termination of drug exposure.

Model II

This model has not been systematically examined with regard to tolerance, although a few studies are available. In the case of alcohol, there is some suggestion that there is independence of tolerance episodes under some conditions. For example, with single exposures to alcohol, acute tolerance does develop (Mellanby 1919; LeBlanc, Kalant and Gibbins 1975); however, if these episodes are separated by periods of at least three days, there appears to be no cumulation of tolerance (LeBlanc 1972).

A parallel phenomenon has been observed in the case of physical dependence on alcohol. A single exposure to alcohol produces observable withdrawal signs as blood level decreases. And as with tolerance, the severity of physical dependence is unaffected by repeated exposures to alcohol if they are spaced at 4-day intervals (LeBlanc 1972). Since single exposures to alcohol are clearly capable of producing both tolerance and dependence, it cannot be argued that failure to demonstrate a cumulative process is due to an inadequate manipulation.

As is evidenced elsewhere in this volume the greatest proponents of Model II are the Goldsteins and their co-workers. Although there are variations in details of these studies, the following generalizations appear to emerge:

- (a) In the case of both opiates and alcohol, tolerance and physical dependence develop in less than 24 hours of continuous exposure.
- (b) For both opiates and alcohol, tolerance and physical dependence disappear within a few days following cessation of treatment.
- (c) Independent of the duration of a single exposure to alcohol or an opiate, if the exposures are spaced at intervals of sufficient duration (16-24 hours) no accumulation of tolerance or dependence is observed.

In summary, there is no shortage of data consistent with the requirements of Model II.

Model III

One of the earliest findings in support of Model III was reported by Decsi, Várszegi, and Méhes (1961) who studied tolerance to tremorine. They found that tolerance developed more rapidly during a second cycle of treatment. Unfortunately this brief report provides

insufficient evidence to permit an independent assessment of the data.

A study by Mendelson, Stein and McGuire (1966) provides a much better documented case for Model III, although it was not designed for that purpose. Moreover the degree of experimental control was less than complete. Nonetheless, a group of "dried out" alcoholics was compared to a group of non-alcoholics. Although initial levels of drinking were comparable, the rate of increase was greater among the alcoholics than their non-alcoholic counterparts. This evidence is far from conclusive, since the relationship between tolerance and self administration is unclear, but it is certainly consistent with the requirements of the model.

The most systematic attempt to evaluate Model III with regard to tolerance has been conducted in this laboratory. What appears to be compelling evidence in support of Model III was provided by LeBlanc (1972) and Kalant, LeBlanc and Gibbins (1971b). Tolerance was measured in rats on the moving belt apparatus, which permits a test of motor impairment. A degree of tolerance which initially required seventeen days to develop was evoked in only four days after two cycles of acquisition and loss of tolerance. Importantly, there was evidence that tolerance was completely lost during the seventeen day withdrawal intervals.

Although the rate of tolerance development was profoundly altered, the maximum level of tolerance achieved did not increase with repeated cycles. During the first cycle of tolerance, there was an absolute ceiling on the level of tolerance development. Attempts to increase the level with higher doses were unsuccessful. Even when a group of rats was allowed to recover for as long as three months, there was still a persistent increase in the rate, though not the level of tolerance achieved, during yet another cycle of testing.

In an attempt to determine whether a comparable process applies in the case of opiates, tolerance to the thermic effect of morphine was studied in our laboratory³. In the rat, morphine first briefly lowers temperature, then raises it to a stable hyperthermic level for a more protracted period; the temperature eventually returns to normal. In our experiment, a test dose was administered daily for ten days. During this period the initial hypothermic effect gradually disappeared, and the time to achieve the stable hyperthermic plateau decreased, *i.e.* there was evidence of tolerance. After a recovery period of four weeks, during which no treatment was administered, the cycle was repeated. During this cycle there was a significant increase in the rate of tolerance development.

There are two studies of dependence that are consistent with the requirements of Model III. Branchey, Rashev, and Kissin (1971) fed rats a liquid diet⁴ containing alcohol for three weeks; withdrawal signs occurred only at the end of this period. After a two week period of abstinence the animals were again exposed to alcohol. On this occasion four of eight rats exhibited physical dependence after only four days exposure. This was in contrast to controls that had not received the first exposure to ethanol.

A study by Walker and Zornetzer (1974) focussed on severity of withdrawal signs during repeated cycles of ethanol exposure. Mice made dependent and then withdrawn for two weeks, were then re-exposed to ethanol. After a comparable period of exposure, withdrawal signs were much more severe during the second cycle than they were on the first.

Just as with Model II, there is little difficulty in citing evidence in support of Model III. Clearly, some analysis is required to address this apparent discrepancy.

³Le Blanc and Cappell. Unpublished observations.

⁴Superficially this method of administration may seem to provide a constant level of exposure to alcohol. However, voluntary selection of alcohol in rodents produces intermittently rising and falling drug levels because of the circadian nature of drinking. Thus a study involving this method is more appropriately related to Model III than to Model II.

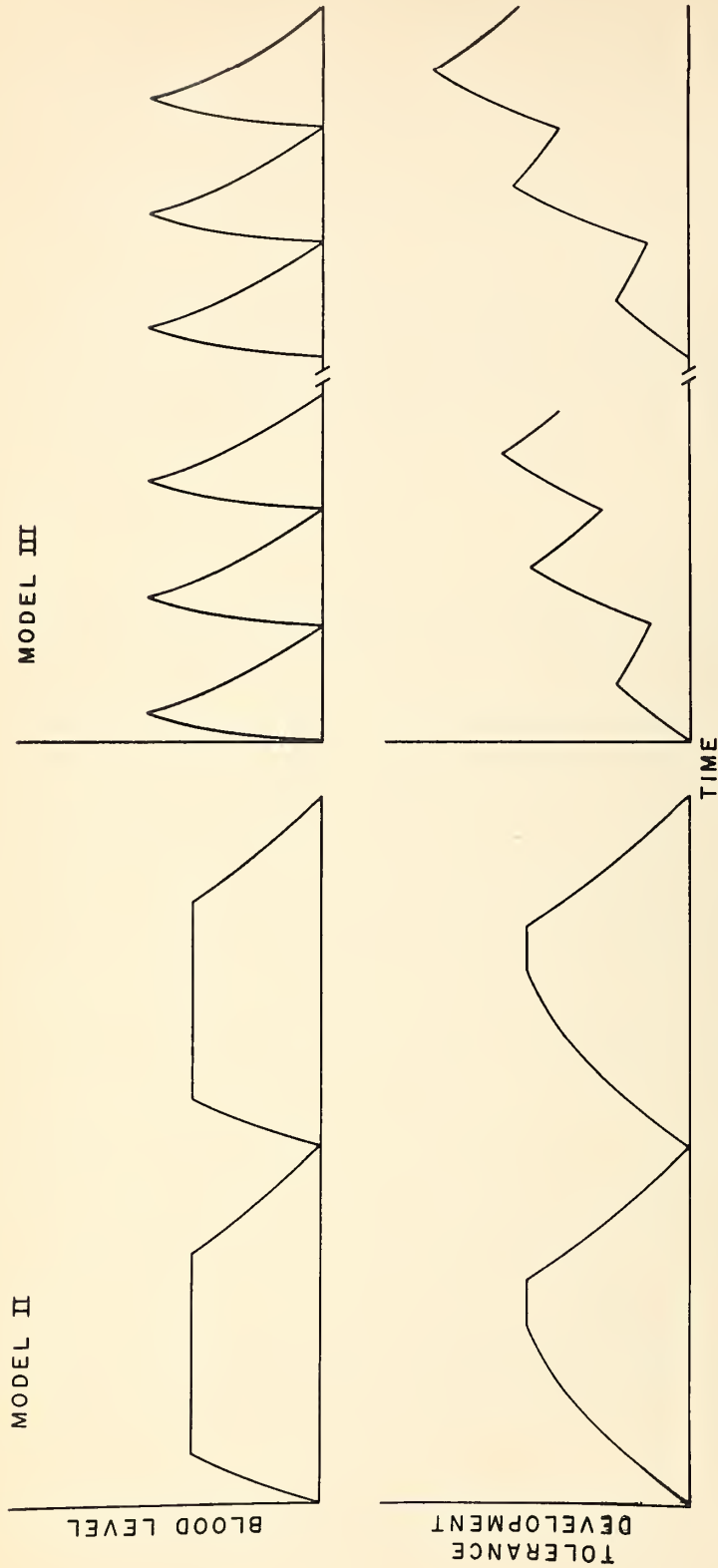


Figure 2. Schematic representations of differences between Models II and III. In Model II blood levels are held relatively constant within a given cycle of drug exposure; in Model III blood levels ascend and descend repeatedly within a cycle. In Model II a new cycle is introduced immediately upon recovery; in Model III a substantial delay intervenes between cycles. Note the differences in slopes of tolerance acquisition in Model III as compared to Model II. A similar description would apply to dependence.

AN ATTEMPT AT RECONCILIATION

Model I provides no serious problems of interpretation. It should not be surprising that if a new cycle of tolerance or dependence is introduced prior to complete recovery from a previous one, there should be a cumulative effect. However, there does appear to be some conflict in the evidence adduced in support of Models II and III. In the former case, previous exposure to drugs had no measurable consequences for the impact of subsequent exposures; in the latter, quite the opposite was true. Resolution of this apparent conflict requires an analysis of the procedures employed in the relevant investigations.

The first procedural difference relates to the manner of drug administration. In studies providing support for Model II, animals have been typically exposed to a relatively constant level of drug for relatively short periods of time before a recovery period is introduced. For example, in the study by Cheney and Goldstein (1971) physical dependence was induced by implanting morphine pellets for 3-7 days. Thus the animals were constantly exposed to the drug. Inhalation of ethanol in the presence of pyrazole is an analogous procedure (Goldstein 1974). In a sense, these procedures represent a single, albeit protracted, exposure to the drug.

In studies providing support for Model III, the pattern of drug administration within a cycle has been quite different. Exposures have tended to be intermittent, with the consequence that there have been repeated wide variations in blood level, ranging from relatively high to relatively low. The contrast in the two types of procedures is evident in Figure 2. This difference could have important consequences for processes of adaptation to the presence of the drug. Perhaps the frequent intermittent stimulation of the adaptive process causes it to consolidate more effectively than does a relatively brief uninterrupted stimulation. Admittedly the argument is speculative, but as any good *ad hoc* analysis should, it can account for all of the existing data.

A second procedural difference has been in the duration of the recovery intervals between cycles of drug exposure. When experimental studies have supported Model II there has been a minimal delay prior to the initiation of a subsequent cycle. For example, in the study by Cheney and Goldstein (1971), dependence was allowed to become virtually maximal during the first cycle. The second cycle was initiated immediately upon recovery from the first. Comparatively short intervals between cycles also characterize the studies by Goldstein and Sheehan (1969); Goldstein, D. (this volume) and Wei and Loh (1972). In contrast, when studies have supported Model III, the interval between cycles has been relatively long, ranging from 11 days (Walker and Zornetzer 1974) in mice to 1 month in rats (Cappell and LeBlanc⁵). Again we can conjecture that the long delay, just like the intermittent stimulation, facilitated a consolidation process which became manifest on subsequent cycles of tolerance and dependence. Possibly these two hypothetical consolidation processes may interact such that both are necessary to generate the type of data consistent with Model III.

There is yet a third difference worth considering. In those studies consistent with Model II, maximal tolerance and dependence have been induced with extreme rapidity, perhaps at the limit of the rate of these processes. To detect an effect of a previous experience on a subsequent one under such conditions may require a degree of measurement sensitivity which is difficult to attain. Alternatively, it may be biologically impossible by whatever means to enhance the rate of a process already functioning at its physiological limit. Studies consistent with Model III have involved processes occurring at

⁵Unpublished observations.

much slower rates, hence obviating both of the previous difficulties.

If this analysis has merit, there is no irreconcilable conflict among the studies that confirm the different models; the data of each class of investigation may be taken at face value as representing genuine phenomena, but phenomena that reflect the involvement of different processes that are engaged by the different procedures which were typically employed. Yet it remains important to ask which schedule of drug administration most closely resembles drug use in "real life". Only rarely is man exposed to drugs of abuse at constant levels for relatively short periods without interruption. Much more common is the pattern of use approximated in the studies that have yielded evidence in support of Model III. Thus, while both classes of investigation have dealt with important processes, it may be that those confirming Model III may be more pertinent to an understanding of the variables governing the processes of tolerance and dependence in man.

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The Behavioural Pharmacology of Addiction: Some Conceptual and Methodological Foci

David A. Downs, James H. Woods,¹ and Mark E. Llewellyn

INTRODUCTION

Rhesus monkeys will self-administer drugs. It is relatively simple to predict which monkeys will become drug-takers. First, find a drug that other monkeys will self-administer. Second, arrange a system so that a monkey can cause the drug to be delivered. Third, watch the monkey take the drug.

Why does the monkey do this? If it is fair to extrapolate from humans to monkeys, we can paraphrase some answers from information about people:

“The manifestation of some monkeys’ dissatisfaction and loss of faith in the prevailing social system, making them feel there is a lack of meaningful alternatives to drug using behaviour.”

“The statements of proselytizing monkeys who proclaim the ‘goodness’ of drugs.”

“The search for different perception and ideas which some monkeys believe they can obtain from mind altering drugs.”

“The belief that ‘medicines’ can solve all problems.”

“Monkeys start and continue to use drugs because they want to do so, not because of some intrinsic nature of the drug.”

“Drug users are not necessarily immature, immoral, irresponsible, socially disadvantaged, alienated, rebellious, or mentally ill. Drug use is a part of the continuum of monkey existence.”

Perhaps it is difficult to account for why monkeys or people take drugs because it is

¹ University of Michigan, Departments of Pharmacology and Psychology, Ann Arbor, Mich. 48104, U.S.A.

difficult to account for why monkeys or people do anything. Is it necessary to use a different account for drug-taking behaviour as opposed to gambling behaviour, television-watching behaviour, or candy-eating behaviour? The answer would seem to depend upon the extent to which the various kinds of behaviour may be described in similar terms, measured in similar dimensions, and controlled according to similar principles.

The purpose of this chapter is to describe drug-taking in terms of the methods and conceptual framework of the experimental analysis of behaviour (e.g. Skinner, 1969). We will address the issues from the vantage point of laboratory investigations of drug self-administration in animals. In the course of our presentation, we will attempt to demonstrate the relevance of basic principles of this analysis to at least some aspects of human drug addiction.

The major principle, of course, is that the frequency of a given behaviour can be a function of the previous consequences of that behaviour. Events which increase the rate of occurrence of a response which they follow are called positive reinforcers. Conversely, an event which increases the rate of occurrence of a response which terminates or postpones it is termed a negative reinforcer. These terms may be used to describe behavioural functions of drugs. Classification of a drug as a positive or negative reinforcer depends upon the effect of the drug when delivered as a behavioural consequence on the future probability of drug-taking behaviour. Other consequences of drug administration, such as a description of the subjective effects of the drug, alterations in neurophysiological activity, or changes in autonomic functions, do not enter into the qualification of a drug as a reinforcer.

A reinforcer need not follow every occurrence of a response in order to control response rate. Intermittent reinforcement may be scheduled on the basis of the number of responses emitted or the amount of time elapsed since the last reinforcement. An alcoholic derelict, for example, may have to rummage through a dozen garbage cans before he finds an object of sufficient value to exchange for a bottle of cheap wine. Thus, behaviour may be maintained with only occasional delivery of reinforcement.

An important feature of different schedules of reinforcement is that they result in patterns of behaviour characteristic of the temporal or response requirements involved. In addition, such characteristic patterns of schedule-controlled behaviour are significant in that they interact with other variables. As we will show later, some drug effects will depend on the schedule of reinforcement controlling behaviour as well as on variables such as the drug itself, the dose, the route of administration, and the pharmacological and behavioural history of the subject.

Schedules of reinforcement may be combined so that they are sequentially or simultaneously in effect. When different schedules of reinforcement operate sequentially, responding is controlled primarily by the schedule in effect at any given time although interactions between sequential schedules may occur. When two schedules are simultaneously in effect, distribution of responding occurs, dependent upon the response requirements of each schedule and the rate of reinforcement, the magnitude of reinforcement, and the type of reinforcer delivered under each schedule. In general, behaviour is comprised of many individual classes of responses. The predominant occurrence of some of these responses can affect the rate of occurrence of other responses, if only by exclusion. Thus, if behaviour required to obtain drug is elaborate and time-consuming, one might expect to see a decrease in the frequency of other behaviours such as working, social interactions, or recreational activity.

When a response is reinforced only in the presence of a certain stimulus, the fre-

quency of responding is increased in the presence of that stimulus. Moreover, responding occurs at different rates in the presence of stimuli that are associated with different frequencies of reinforcement. Such responding is said to be under stimulus control or under the control of discriminative stimuli. Furthermore, stimuli that are associated with reinforcement can become conditioned reinforcers and themselves maintain behaviour.

Drug-related behaviour actually may be composed of sequences of several different behaviours, each of which is maintained by the conditioned reinforcing effects of other stimuli in the sequence. In principle, the last event in the sequence, the administration of a drug, can maintain other related behaviours which may precede it by long time intervals.

Stimuli, including drugs, can have multiple behavioural functions. Events can function simultaneously as reinforcers and as discriminative stimuli. For example, an injection of drug may maintain self-administration in an addict and simultaneously operate as a discriminative stimulus for sexual intercourse if drug-taking typically precedes sexual contact for that individual. On the other hand, drug administration may set the occasion for avoidance of people who are likely to punish the post-injection behaviour of the addict.

In addition to reinforcing and discriminative functions, response-eliciting functions are often especially apparent with drug stimuli. Drug-elicited responses are consequences of drug administration which occur independently of the contingency between behaviour and drug injection. Emesis, salivation, cardiovascular changes, and neurophysiological effects are examples of responses which may be elicited by various drugs. In general, such effects can be observed upon acute administration. Occasionally, however, elicited responses are observed only after repeated drug administration. An example of the latter case is the sensation (tactile hallucinations) of live insects or animals crawling under the skin frequently associated with chronic cocaine or amphetamine administration (Woods and Downs, 1973).

The behavioural functions of such elicited responses may be quite complex. In some cases, drug-elicited events such as nausea or emesis may function similarly to punishing stimuli. However, it is important to determine not only whether a particular drug function occurs. In other cases, however, such effects may function as conditioned reinforcers. An example of the latter would be reflected in the narcotic addict's description of nausea associated with narcotic injection as a "good sick." Finally, drug-elicited responses themselves may become conditioned to stimuli associated with drug administration. Collins and Tatum (1925), for example, demonstrated that salivation elicited by morphine injection in dogs could, after repeated injections, be produced merely by the sight of a syringe or the presence of the experimenter. Other examples of conditioned drug effects and how such effects can influence operant behaviour maintained by drug and non-drug reinforcers have been discussed more extensively by Goldberg (1970).

The preceding brief overview of various stimulus functions of drugs suggests that drug-taking may at least be described consistently within the framework of the experimental analysis of behaviour. Let us now examine some of the behavioural functions of drugs in greater detail.

DRUGS AS REINFORCERS

As positive reinforcers, there are a number of ways in which many drugs appear to function similarly to non-drug reinforcers. There are, of course, the obvious and impor-

tant similarities which are the basis for common operational classification as reinforcers; namely, drugs can increase the probability of behaviour when they are delivered as a behavioural consequence. Rhesus monkeys, for example, may be surgically prepared with chronic indwelling venous catheters so that injections of drugs can be delivered directly into an animal's bloodstream. It is then possible to arrange a system so that an injection of drug is automatically delivered whenever a monkey emits some specific response, e.g. pressing a lever. When the responses result in injections of any of a wide variety of drugs, the frequency of responding will increase. The increase in frequency (probability) of responding defines the response-contingent drug as a positive reinforcer.

The establishment and maintenance of responding reinforced by drug is comparable in principle to the establishment of responding reinforced by a variety of non-drug stimuli. However, it is important to determine not only whether a particular drug functions as a reinforcer, but also whether similar parametric functions apply for drug as well as non-drug reinforcers. Magnitude of reinforcement is one parameter which might generally influence response probability. For this reason, various experimental procedures have been developed to compare the effects of different reinforcement magnitudes. In an example of one procedure, subjects are presented with two or more concurrently available response alternatives (e.g., different response keys or levers). Each alternative is typically associated with the delivery of a different magnitude of a reinforcing stimulus; that is, responding on one alternative is occasionally reinforced by delivery of one magnitude of a reinforcer. At the same time, responding on the other alternative is occasionally reinforced by delivery of a different magnitude of a reinforcer. The general result of this concurrent schedule procedure is that responding is distributed among the response alternatives in approximately the same proportions as the relative amount of reinforcer obtained by responding on each alternative (Herrnstein, 1970). For example, if twice as much of a reinforcer is delivered as the consequence of responding on alternative A than on alternative B, then one would expect twice as much responding on alternative A, assuming other factors equal.

The proportional distribution of responding and obtained reinforcement is called a matching function (e.g. Herrnstein, 1970). Approximations of matching relationships have been demonstrated for parameters of food reinforcement, such as duration of feeder presentation (Brownstein, 1971; Catania, 1963), sucrose concentration (Walker and Hurwitz, 1971), and relative frequency of food presentation (Stubbs and Pliskoff, 1969). Matching functions also have been shown for magnitude of brain stimulation reinforcement using a variation of the concurrent procedure (Pliskoff and Hawkins, 1967). Concurrent procedures have been extended to compare qualitatively different reinforcers, as in the case of food and electrical brain stimulation (Hollard and Davison, 1971). In general, it appears that the matching relationship may be a rather fundamental property of concurrent schedules, which are, in effect, experimental models of preference and choice.

Experiments in our laboratory have recently examined drug reinforcement magnitude using similar techniques (Iglauer and Woods, 1974). Figure 1 shows a comparison of responding for variable doses (mg/kg/injection) of cocaine associated with one response lever against fixed doses associated with a second lever in a rhesus monkey. The diagonal line represents a perfect matching relationship. The filled circles represent the actual data obtained when a dose of 0.1 or 0.05 mg/kg/injection was always associated with one (fixed) lever as compared to each of various doses ranging from 0.025 to 0.4 mg/kg/injection associated with the other (variable) lever. Figure 1 demonstrates that when the

relative amount of drug obtained by responding on the variable lever was equal to that obtained on the fixed lever (indicated as 0.5 on the abscissa), the amounts of responding on each lever were approximately equal (indicated as 0.5 on the ordinate). As the amount of drug obtained on the variable lever increased above that obtained on the fixed lever, the relative amount of responding on the variable lever increased proportionately. Conversely, when the relative amount of drug obtained on the variable lever decreased below that obtained on the fixed lever, the amount of responding on the variable lever decreased proportionately.

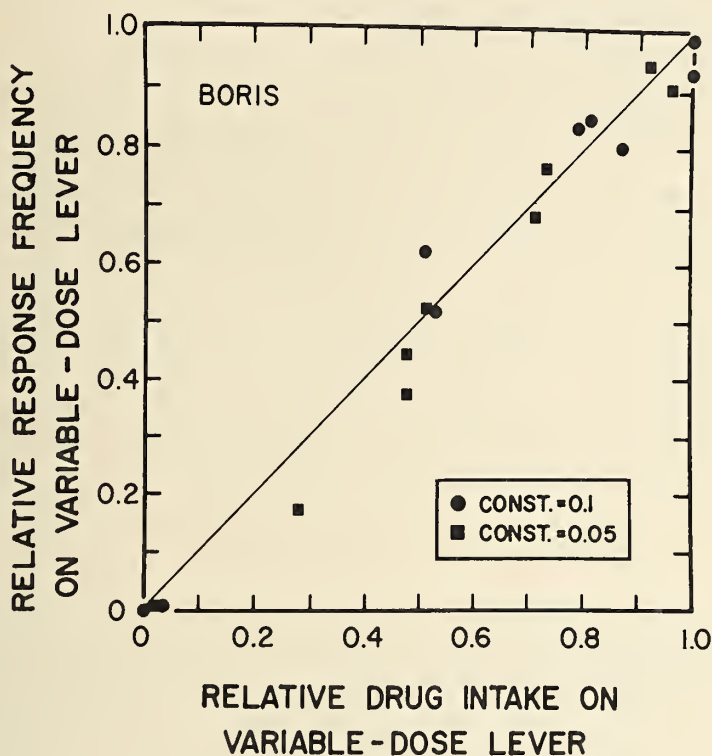


Figure 1. Matching of relative response frequency to relative obtained reinforcement in one monkey. The diagonal line theoretically represents perfect matching. Data points were obtained by comparisons of a constant dose of 0.1 or 0.05 mg/kg/injection on one (fixed) lever with each of 5 different doses ranging from 0.025 to 0.4 mg/kg/injection on a second (variable) lever. Equal variable-interval 1-minute schedules were concurrently in effect on both levers (from Iglauer and Woods, 1974).

The above experiment represents a clear demonstration of matching with cocaine reinforcement. Eventually, such experiments may compare particular drug reinforcers against other drug reinforcers or non-drug reinforcers. At present, however, the ways in which various aspects of behaviour controlled by drugs interact with overall behavioural repertoires have only begun to be examined in the laboratory. In contrast, human behaviour is probably controlled by multiple contingencies of reinforcement which interact both sequentially and concurrently. Understanding drug effects in such interactions undoubtedly will be important in the modification of drug-taking behaviour.

In addition to the concurrent-schedule procedures, other experiments have shown similar relationships between response rate and reinforcement magnitude for drug and non-drug reinforcers. For example, rate of responding for sweetened water under fixed-

interval schedules has been shown to be directly related to sucrose concentration (Stebbins, Mead, and Martin, 1959). Likewise, Balster and Schuster (1973) have demonstrated similar effects of cocaine dose on response rates under a fixed-interval schedule of drug reinforcement. Goldberg (1973) directly compared effects of magnitude of food reinforcement and cocaine or d-amphetamine dose on response rates under various schedules of reinforcement in monkeys and found "striking parallels between food-maintained and drug-maintained responding...over a wide range of parameter values when they are studied under similar behavioural schedules". Other parallels have been found for food and cocaine when schedule requirements were the same for both reinforcers in rats (Pickens and Thompson, 1968).

Reinforcement magnitude, of course, is not the only parameter which might be expected to be important in drug-behaviour interactions; it is merely one aspect of drug self-administration research which has received considerable attention in recent years. There are other operational dimensions along which drug and non-drug reinforcers should be compared. Examples of such dimensions are immediacy of delivery (delay of reinforcement), route of administration, strength of associated conditioned reinforcers, suppression of responding by punishment, or effects of deprivation. The extent to which drug-reinforced responding may be suppressed by punishment could be of special interest since there are indications that some drugs (e.g. barbiturates and minor tranquilizers but not amphetamines or morphine) may attenuate punishment (Geller, 1962; Geller and Seifter, 1960, 1962; Geller, Bachman and Seifter, 1963; Geller, Kulak, and Seifter, 1962). If the same drugs which attenuate punishment also function as reinforcers, attempts at aversive control of drug-taking might produce very interesting effects.

Historical and Current Influences

Hoffmeister and Schlichting (1972) have demonstrated that previous self-administration experience with a particular class of drugs can modify the subsequent self-administration of drugs of different classes. Rhesus monkeys with histories of responding reinforced by a narcotic (codeine) emit higher rates of responding for other opioids (e.g., morphine, pentazocine) than do monkeys previously reinforced with cocaine. In contrast, monkeys with cocaine reinforcement histories show greater intake of d-amphetamine than do monkeys with codeine histories (Schlichting, Goldberg, Wuttke, and Hoffmeister, 1971). Moreover, certain drugs (pentazocine, propiram) may function as either positive reinforcers or negative reinforcers in rhesus monkeys, depending upon the presence of morphine-type physical dependence (Goldberg, Hoffmeister and Schlichting, 1972). Thus, pharmacological history clearly can be an important factor in the effects of a drug on behaviour.

On the other hand, Woods, Downs, and Carney (1975) have noted that the same drug (naloxone) may maintain behaviour which avoids or terminates its delivery under one set of schedule conditions and later maintain behaviour which results in its delivery under a slightly different set of schedule conditions in the same animals. In this case, behavioural history and current schedule conditions clearly are primary determinants of the behavioural effects. Therefore, in addition to the previous history of the animal, variables which currently control behaviour must be considered.

With drug reinforcers and non-drug reinforcers, different schedules of reinforcement control distinctive rates and patterns of responding. Not only are different response rates and patterns controlled by different schedules of drug reinforcement, but schedules of

reinforcement can also affect drug intake. Weeks and Collins (Weeks, 1962; Weeks and Collins, 1964) have reported decremental effects of increasing fixed-ratio values on morphine intake in rats. Weeks and Collins (1964), for example, found that an increase in response requirements from 1 response/injection (FR1) to 10 responses/injection (FR10) resulted in a decrease of about 40% in average daily morphine intake. Goldberg, Hoffmeister, Schlichting, and Wuttke (1971a) reported similar effects of ratio requirements on self-administration of pentobarbital in monkeys. Depending upon the dose/injection, Goldberg *et al.* found that an increase in response requirements from FR1 to FR10 could reduce pentobarbital intake to as little as one-third of the previous level. On the other hand, cocaine intake remains fairly constant over a wider range of schedule and dose parameters (Pickens and Thompson, 1968; Goldberg *et al.*, 1971a). Unfortunately, comparable information for non-drug reinforcers is not available. It would be interesting to know if food intake or water intake showed similar effects of response requirements under comparable conditions.

The above findings do not necessarily mean that morphine as a reinforcer is capable of sustaining only a modest number or low rate of responses. The upper record of Figure 2 shows the performance of one animal under a second-order schedule when the first FR10 completed after 10 minutes resulted in an intravenous morphine injection and the opportunity for two additional morphine injections. In the lower record, the time between each instance of morphine availability was thirty minutes. In each of these cases, the number of responses per injection of morphine was far greater than the minimal requirement to obtain an injection of drug. An even more striking example of the maintenance of substantial behavioural outputs for single morphine injections has been provided by Goldberg and Morse (1973), who employed a somewhat similar schedule in examining responding reinforced by intramuscular injection of morphine or cocaine in rhesus monkeys.

The fact that modest increments in response requirements can produce substantial decrements in the intake of certain drugs, yet under other circumstances responding for the same drugs can be maintained for relatively long intervals by single drug injections, further illustrates the principle that behavioural actions of drugs depend upon pharmacological characteristics as well as properties of ongoing behaviour (e.g. Kelleher and Morse, 1968). Thus, concepts such as "reinforcement efficacy" must be qualified for a given drug under a particular set of experimental conditions and must not be expected to imply absolute properties which will hold across all behavioural conditions.

Drug Availability and Patterns of Drug Intake

In the preceding discussion, we pointed out a variety of conditions under which drug reinforcers appear to function similarly to non-drug reinforcers. We also noted that certain drugs seem to interact with responding in ways which are not clearly analogous to the effects of more "conventional" reinforcers. The influence of schedule value on morphine or pentobarbital intake is but one example of such an interaction. Another example is the effect of duration of drug availability on overall patterns of drug self-administration. For example, when drug availability is unlimited, the amount of cocaine self-administered over days may show fairly large fluctuations (Deneau, Yanagita, and Seevers, 1969). Similar effects occur with alcohol self-administration (Deneau *et al.*, 1969). These patterns, in some cases, have been remarkably similar to reported patterns of human self-administration of the same drugs. When drug availability is restricted to

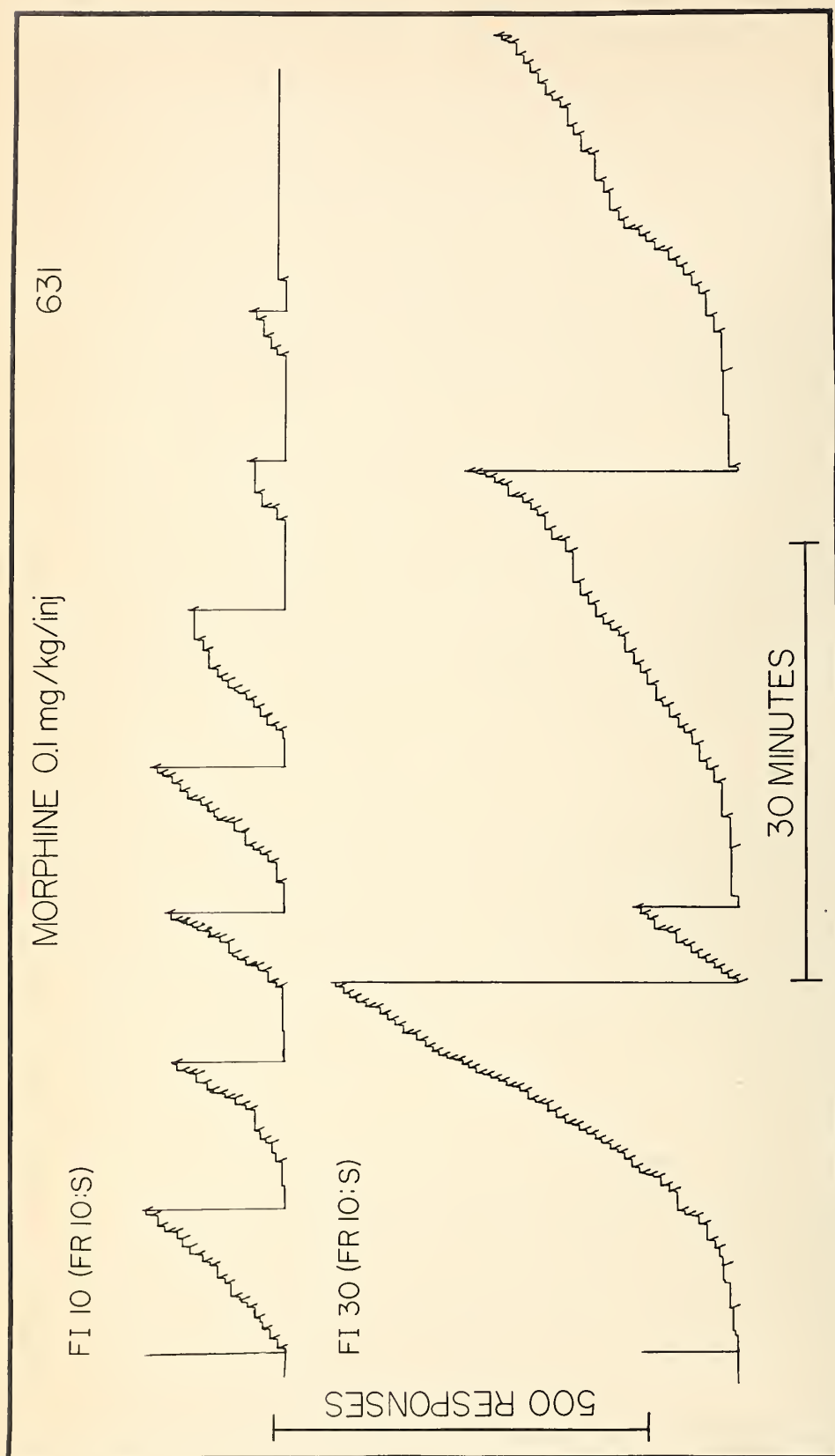


Figure 2. Cumulative records of responding in one monkey (631) under a second-order schedule of morphine reinforcement. In the upper record, every tenth response resulted in a 0.5-sec flash of light (FR10:S); the first FR10:S completed after 5 minutes resulted in an injection of morphine (0.1 mg/kg/injection). Oblique deflections of the response pen indicate light flashes; the response pen reset after each injection. In the lower record, three morphine injections were available following every tenth response at the end of each thirty-minute fixed-interval. The response pen reset following about 535 responses or the last injection.

limited periods of access (e.g. 3 hours/day), drug intake may show more stability across sessions (e.g., Woods, Ikomi, and Winger, 1971).

While limited drug availability may stabilize total drug intake, there still may be differences among drugs in local patterns of drug-reinforced responding. With cocaine, injections of drug are typically self-administered at regular intervals within sessions (Pickens and Thompson, 1968). With opiates, on the other hand, there is usually a negatively accelerated distribution of injections within sessions in rhesus monkeys (Downs and Woods, 1974; Hoffmeister and Schlichting, 1972). With barbiturates, injections tend to be self-administered in bursts with more or less erratic pauses between groups of injections (Winger, Stitzer, and Woods, 1971). At present, the variables responsible for these differences among drugs are not clear. To the extent, however, that factors which control different patterns of drug intake under experimental situations are similar to those which control patterns of human drug self-administration, then a greater understanding of such variables should be of value in efforts to alter or eliminate those behaviour patterns in human drug abusers.

Drug-taking and Aversive Control

Thus far we have discussed reinforcing functions of drugs only in terms of positive reinforcement. On the other hand, it has been suggested that the drug-seeking behaviour of human addicts is controlled not only by positive reinforcement, but also by negative reinforcement associated with avoiding or terminating abstinence in the case of drugs which produce physical dependence (Seevers, 1968; Skinner, 1969; Wikler, 1973). However, it is difficult for such theoretical accounts to distinguish instances of positive reinforcement from those of negative reinforcement, since in all cases the behaviour to be accounted for is the self-administration of a drug. Thus, behaviour maintained by the response-contingent presentation of a stimulus is said to be under the control of positive reinforcement. The fact that this may or may not occur under conditions of deprivation (e.g. drug abstinence) is not relevant to the operational definition of positive reinforcement.

Nevertheless, to the extent that narcotic antagonist administration is analogous to deprivation-induced abstinence in narcotic-dependent animals (Woods, Downs and Villarreal, 1973), it is possible to examine such negative reinforcement contingencies.

In an experiment demonstrating negative reinforcement with narcotic antagonist (Downs and Woods, 1973), rhesus monkeys were trained to self-administer morphine during various portions of each day. At other times, the monkeys were required to press a lever to interrupt a continuous infusion of naloxone (0.001 mg/kg/min). Initially, each response stopped the naloxone infusion for one minute. When stable performance developed, the response requirements were increased until FR 20 responding was reliably maintained. Figure 3a shows a cumulative record of a session under the FR 20 schedule of escape. The preceding session of morphine self-administration is also included for comparison.

Another procedure involves both avoidance and escape. Again, monkeys were trained to self-administer morphine during various portions of each day. During other periods, the monkeys were exposed to a naloxone avoidance-escape procedure. In the avoidance-escape procedure (Figure 3b), a warning light preceded an injection of the narcotic antagonist. The monkeys then could avoid the scheduled injection by completing a required number of responses within thirty seconds after the warning light onset. Under

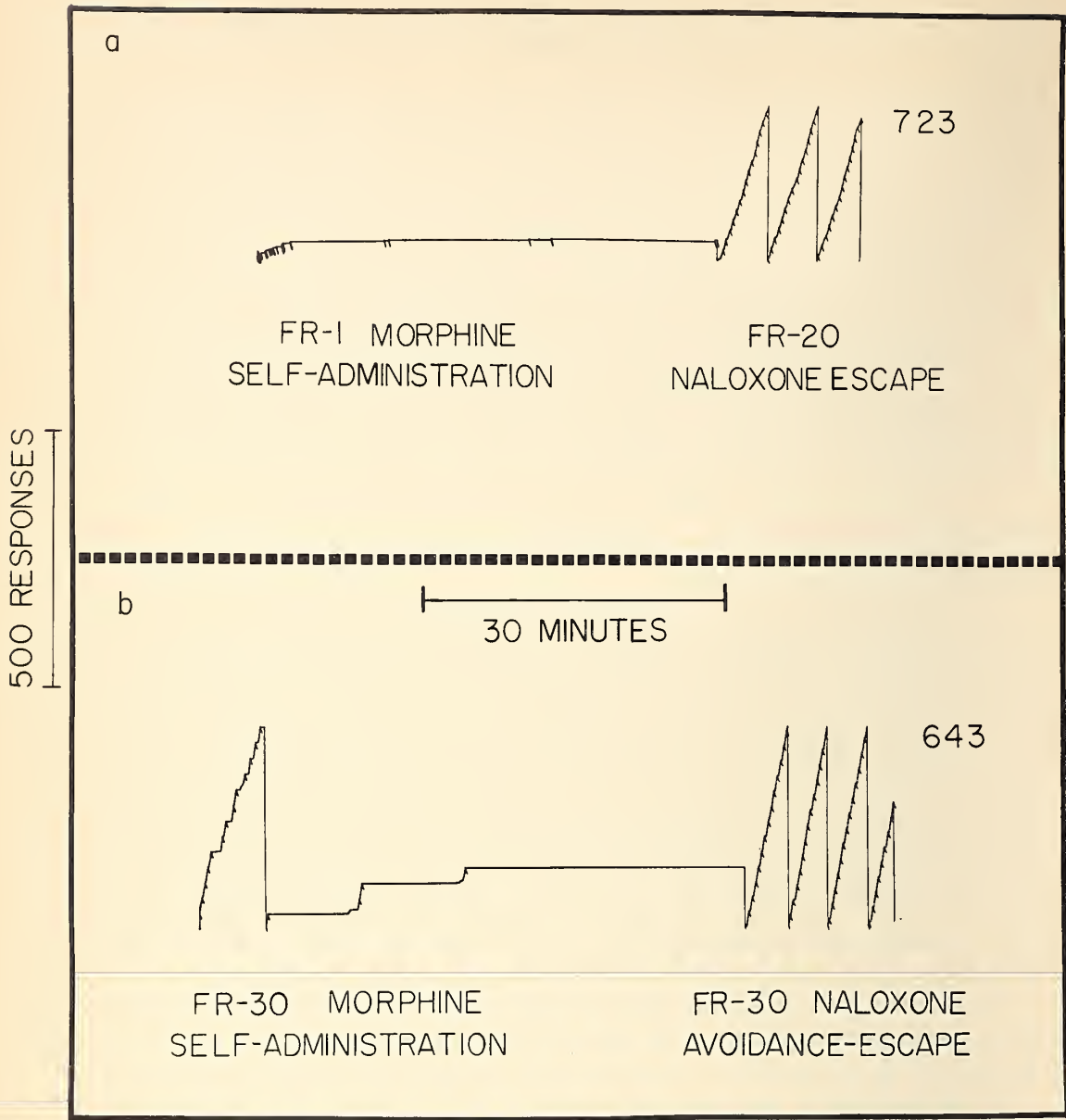


Figure 3. (a) Cumulative response records of FR1 morphine self-administration (0.1 mg/kg/injection) and FR20 escape from naloxone (0.001 mg/kg/minute) in one rhesus monkey (723). In the morphine session, each lever-press (response) stepped the response pen upwards. Oblique deflections of the response pen indicate morphine injections. The paper drive did not run during injections. In the naloxone-escape session, a continuous infusion of naloxone was interrupted for 1 minute following every 20 responses. Each session lasted one hour. Two hours intervened between the morphine self-administration session and the naloxone-escape session. (b) Cumulative response records of FR30 morphine self-administration (0.1 mg/kg/injection) and FR30 avoidance-escape from naloxone (0.001 mg/kg/injection) in one monkey (643). In the naloxone avoidance-escape session, completion of 30 responses within 30 seconds resulted in a one-minute timeout. Failure to complete 30 responses within 30 seconds resulted in an injection of naloxone. In the session shown, all naloxone injections were successfully avoided.

the avoidance-escape procedure, responding is maintained at relatively high rates to avoid the delivery of narcotic antagonists (Goldberg *et al.*, 1971b; Downs and Woods, 1973).

Narcotic antagonists also can function as punishers (Woods *et al.*, 1973). For example, when antagonist administration is made contingent upon narcotic self-administration, such responding is suppressed. Furthermore, the response suppression extends into subsequent sessions when antagonist is no longer administered (Woods and Villarreal, 1971). Such effects represent additional functional similarities between drug and non-drug stimuli. Although it is tempting to use the above findings with narcotic antagonists to support theories of aversive control of drug-taking in humans, the extent to which this is possible depends upon the extent to which one is willing to accept the functional equivalence of a state (*i.e.*, deprivation from drug) and a drug which can elicit responses characteristically emitted in that state.

Interactions between narcotics and narcotic antagonists are of interest in view of clinical findings that narcotic antagonists may be useful in treatment of human opiate addicts. An assumption in such treatment programs is that the "reinforcing effects" of narcotics will be "blocked," and therefore the addict's drug-seeking behaviour will be extinguished as a consequence of non-reinforcement. However, in view of the variety of behavioural functions of narcotics and narcotic antagonists (Woods *et al.*, 1974), it is unlikely that extinction alone will entirely account for behavioural changes that antagonist treatment programs may effect. Again, continued experimental investigation is necessary for an understanding of how processes of negative reinforcement, punishment, and extinction may control (*i.e.*, increase, maintain, or decrease) drug-taking and the relevance of such phenomena for modification of that behaviour.

Control of Drug-taking by Non-drug Reinforcers

Reinforcing functions of drugs cannot account completely for all drug-taking in humans. First, there are drugs which are abused by humans which have not been shown to be reinforcers in self-administration experiments in animals. Even with drugs which have been shown to function as reinforcers in animals, drug-taking may be maintained by factors other than primary reinforcing properties of those drugs. These "other" factors, for example, must account for an individual's initial experience with the drug. Therefore, we must consider motivational sources other than drugs themselves. In drug self-administration experiments, we sometimes "bait" response levers with raisins or other sweets in order to increase the initial probability of emitting a lever-press response. An obvious analogy in the case of human drug-taking would be a situation in which social reinforcement is made conditional upon drug self-administration. In both the experimental case described above and the human situation, the initial delivery of drug is a consequence of behaviour controlled by non-drug variables. In such cases, however, it is usually necessary only to induce a few responses (which result in drug injections) before the response-drug contingency functions to maintain the behaviour. Thus, the effectiveness of this procedure in rapidly initiating drug self-administration often can be attributed to potent reinforcing properties of the response-contingent drug. On the other hand, it is not necessary that a drug have such properties in order to maintain self-administration. Rodents, for example, normally avoid strong ethanol solutions when pure water is available. Keel (1969) has demonstrated, however, that oral ethanol consumption in rats could be maintained when the consequence of licking a drinking tube was the delivery of food pellets. When the ethanol-food contingency was not in effect, ethanol drinking was not maintained. It is similarly possible to maintain oral ethanol consumption

in rhesus monkeys when licks on a drinking tube result in shock-avoidance (Mello and Mendelson, 1971).

These examples illustrate how drug intake can be initiated and maintained by non-drug positive reinforcement or negative reinforcement regardless of the reinforcing properties of a drug itself. It is not unreasonable to assume that initiation and/or maintenance of some drug-taking in humans also may be a function of consequences other than a drug's primary reinforcing effect. An important point, however, is that the same general conceptual and methodological framework is applicable whether drug-taking is maintained by drug or non-drug reinforcers.

An additional area of research is the phenomenon of "adjunctive behaviour." Falk (1961) discovered that under certain schedules of food delivery, animals showed dramatic increases in collateral consumption of fluid. Various investigators have extended these findings to include consumption of alcohol (Lester, 1961; Falk, Samson, and Winger, 1972) and morphine solutions (Leander and McMillan, 1973). Thus, adjunctive drinking has been employed as a tool to induce voluminous consumption of drug solutions which may not be consumed using other methods. The restrictions of the temporal conditions under which such phenomena are observed, however, require restraint in attempts to draw relevance to phenomena of drug-taking in humans. Nevertheless, the principle that the probability of a given behaviour may be dramatically altered as a function of the schedule of reinforcement or schedule of non-contingent stimulus presentation controlling some other behaviour has important implications in functional analyses of drug-taking as well as in the analysis of behaviour in general.

Pharmacological Characteristics of Drug Reinforcers

We have emphasized that stimuli which increase and maintain responding by their presentation, termination, or nonoccurrence are reinforcers. The addition of a number of drugs to the class of events that function as reinforcers emphasizes the plethora of events that may so function. Likewise, it points to the difficulty of finding a common effect other than the reinforcing property. For example, drugs that stimulate or anesthetize function as reinforcers; drugs that attenuate nociception or drugs that counteract these effects also function as reinforcers. The broad description of drugs as central nervous system stimulants or depressants is no more appealing to distinguish among reinforcers than it is to describe other behavioural effects (e.g., Dews, 1962).

Nevertheless, the absence of readily apparent common effects of reinforcing drugs should not allow us to overlook other important characteristics that drug reinforcers might share. For example, if a given stimulus functions as a reinforcer, it is generally most effective when delivered rapidly following a discrete response. When drugs are considered in this light, any physical-chemical variable (e.g., high lipid solubility, low electronic charge, or small size) that would facilitate rapid onset of behavioural action should serve to increase its effectiveness as a reinforcer. Likewise, utilization of routes of administration that favor rapid action should facilitate the effectiveness of drug reinforcers. Nevertheless, when rapidity of onset of behavioural action as well as the capacity to function as a reinforcer have been examined, rapid onset of behavioural action appears to be an insufficient condition (Carney, 1973; Tessel, 1974; Woods and Tessel, 1974). Moreover, it is clear that onset of effect may be postponed on the order of a few minutes since intramuscular morphine injections will maintain schedule-controlled responding (e.g., Goldberg and Morse, 1973).

Often with drugs as reinforcers, the duration of a drug's behavioural action may appear to be longer than conventional reinforcers such as food, water, or electric shock. Thus physical-chemical variables that contribute to the termination of a drug's action by metabolism or distribution to inactive sites in the organism will be important when repeated injections are given. Nevertheless, small doses of some drugs appear to maintain rates of responding comparable to other reinforcers (Woods and Schuster, 1971; Goldberg, 1973; Downs and Woods, 1974; Pickens and Thompson, 1968). When larger drug doses are used, rates of responding are often much lower. Thus the rate-reducing effects of large amounts of a drug reinforcer may be due to cumulative effects which either incapacitate the subject or render ineffective the drug-behaviour contingency. Our paucity of information on wide ranges of reinforcer magnitudes with a number of drug and non-drug reinforcers makes it difficult to evaluate if there are systematic differences between drugs and other stimuli in this respect. The behavioural effect of a drug upon repeated delivery will, of course, be a function of dose, delivery regimen, and route. The interactions between such pharmacological and behavioural variables have yet to be examined in any systematic way.

Perhaps commonalities among drug reinforcers must be sought in terms of their effects on some discrete neurophysiological or neurochemical processes. For example, although most central nervous system actions of drug reinforcers are poorly understood, at least some of the actions are assumed to depend upon neurotransmitters. However, the specific functions of neurochemicals in the central nervous system are difficult to evaluate. The relation of neurotransmitters to behaviour is currently of central concern, but little consensus has been gained. Thus, when any one of a drug's behavioural effects is said to depend upon one neurochemical as opposed to another, a natural skepticism is likely to arise (e.g., Dews, 1962; Mandel and Spooner, 1968). Nevertheless, given the presumed general importance of neurotransmitters, it is inevitable that considerable attention will be paid to their relationships to drug reinforcement. However, assuming that the physiological mechanisms of drug reinforcement are the same as those which "mediate" other reinforcing events, such information may be of little value in the treatment of drug abuse. That is, it is not likely that extirpation of brain regions which subserve reinforcement could become accepted treatment for addiction, since such measures would certainly have dire general consequences.

Nevertheless, elucidation of such relationships would be useful. For example, we might be able to predict which drugs would be reinforcers on the basis of how they affect certain neurochemical processes. It may even be possible to develop *in vitro* models for predicting drugs of abuse, although such techniques appear far from present reality.

A Note on Relapse

Relapse is a term generally used to describe drug-taking after a period of abstinence from drug-taking. As Mello (this volume) has noted, explanations of this phenomenon often are based upon speculations about underlying primary or conditioned abstinoid states. Presumably, such states are consequences of previous drug-taking (e.g. Wikler, 1973; Ludwig and Wikler, 1974). Indeed, there is evidence that various aspects of the narcotic abstinence syndrome can become conditioned to environmental stimuli (Irwin and Seevers, 1952; Goldberg, Woods, and Schuster, 1969; Goldberg and Schuster, 1967; 1970). Moreover, there is some evidence for the persistence of long-term physiological changes in post-dependent rhesus monkeys based upon protracted sensitivity to the narcotic antagonist

nalorphine (Goldberg and Schuster, 1969). Thus, it is conceivable that the reinforcing strength of a narcotic may actually be enhanced in post-addicts.

On the other hand, it is not absolutely necessary to postulate such an intervening mechanism. For example, as we pointed out earlier, the reinforcing function of a drug cannot account for the first drug-taking experience in an individual. Thus whatever factors originally led to drug-taking are likely to be influential in subsequent "relapse" to drug-taking. Moreover, the direct reinforcing functions of drugs should not be expected to be diminished simply because the reinforcing drugs were made inaccessible for some period of time. Finally, environmental stimuli which previously were associated with drug reinforcement (and subsequently came to control drug-taking) likewise would not be expected to become ineffective merely because of drug unavailability. So it should not be surprising that when a post-addict is exposed to environmental stimuli which previously controlled drug-taking, that behaviour is emitted once again. When the behaviour is emitted, the consequence, of course, is administration of drug. Drugs which function as reinforcers increase the future probability of that behaviour and the result may be described as relapse.

We do not intend here to dismiss the potential importance of persistent abstinence phenomena, whether conditioned or based upon long-term physiological changes; rather, we suggest merely that such mechanisms are not necessary to account for relapse. Thus, relapse with drugs which are not known to produce physical dependence (e.g. cocaine, cannabis derivatives) can be described in the same framework as relapse with those which do result in abstinence phenomena.

The import of this discussion for treatment programs has been discussed in detail by Goldberg (1970). Briefly, Goldberg points out that it is necessary to extinguish conditioned stimuli associated with drug reinforcement. Moreover, the behaviour which immediately culminates in drug intake should be extinguished if possible; in the case of opiates, this might be accomplished with the aid of narcotic antagonists such as naloxone, naltrexone, or cyclazocine. Finally, therapy should ensure that a substantial repertoire of behaviour other than, and incompatible with, drug-taking is established and maintained (see Hunt and Azrin, 1973).

THE RELATION OF PHYSICAL DEPENDENCE AND TOLERANCE TO DRUG-TAKING

Physical dependence and tolerance are consequences of the repeated administration of certain drugs (e.g., alcohol, opiates, and barbiturates). Physical dependence and tolerance may develop regardless of the contingency between behaviour and drug administration. Reinforcement, on the other hand, describes an increase in the probability of a given behaviour as a consequence of the response-contingent occurrence of some event.

Drug reinforcers can maintain behaviour despite the absence of detectable physical dependence (Woods and Schuster, 1971; Schlichting *et al.*, 1971). Moreover, drugs which do not appear to produce physical dependence also can be potent reinforcers, e.g., cocaine (Woods and Downs, 1973). Thus, physical dependence clearly is neither necessary nor sufficient to account for drug reinforcement. It has been suggested, however, that once an opiate addict becomes physically dependent, tolerance may also develop to the "directly reinforcing effects" of opioids (Wikler, 1973). Thus the primary determinant of continued drug-taking becomes avoidance or termination of abstinence. Although this conceptualization has intuitive appeal, tolerance to drug reinforcement has never been demonstrated.

The roles of physical dependence, abstinence, and tolerance in the present formulation can be viewed as dynamic rather than causal variables. For example, deprivation from drug in physically dependent animals could possibly result in an enhancement of the effectiveness of subsequent presentations of a drug reinforcer or associated stimuli. Such a parametric change could be analogous to an effective change in the amount of reinforcer in non-deprived animals. Along these lines, Thompson and Schuster (1964), Schuster and Woods (1968) and Woods and Schuster (1971) reported that deprivation from morphine in dependent monkeys resulted in increased response rates in the subsequent presence of stimuli previously associated with morphine. In these cases, increased response rates were not correlated with a change in the rate of morphine delivery. In contrast, morphine-reinforced responding that is directly correlated with morphine intake does not increase following from 11 to 96 hours of deprivation (Woods *et al.*, 1973) even though the severity of the withdrawal syndrome is maximal at 48-72 hours of deprivation in the rhesus monkey (Seevers and Deneau, 1963). Clearly the severity of withdrawal signs and the amount of morphine self-administered are not closely related over various periods of morphine deprivation. These studies suggest that the major effects of deprivation from morphine are manifested as changes in response probabilities controlled by stimuli associated with morphine.

Tolerance may be viewed in much the same way as physical dependence: tolerance to a drug simply may represent a change in effective reinforcer magnitude. It should be kept in mind that tolerance is generally described by a shift to the right in the dose-effect curve for a drug. Thus, when one speaks of tolerance to a drug's "reinforcing effect" what is actually meant is tolerance to the effects of a particular dose (amount of drug) rather than the elimination of reinforcement. As we noted above, however, such tolerance has not been demonstrated with respect to drug reinforcement. Quite to the contrary, Carney (1973) has shown that tolerance could develop to disruptive effects of opiates on food-reinforced behaviour while codeine-reinforced responding in the same animals remained constant over the same time course. Winger, Stitzer, and Woods (1971) similarly reported that the duration of pentobarbital anesthesia was markedly shortened after daily self-administration of a variety of barbiturates despite the apparent absence of tolerance to the barbiturates' reinforcing effects over the course of the experiment.

These findings are consistent with the fact that tolerance can develop at different rates and to different extents to various effects of a given drug (Seevers and Woods, 1953). Thus, an increase in the rate of drug-maintained behaviour over the course of a self-administration experiment would be difficult in most cases to interpret simply as tolerance to drug reinforcement because tolerance also develops to other behavioural effects, e.g. response disruption. Indeed, based upon the above evidence, it would appear that the reinforcing effects of opiates and barbiturates show less tolerance than some of their other behavioural effects.

SUMMARY

This chapter has been an attempt to describe an experimental analysis of drug-taking. The approach is derived from a more general system which analyzes the probability of behaviour as a function of the prior consequences and context of similar behaviour. Within the methods and principles of this analysis, many behavioural effects of drugs are essentially equivalent to those of nondrug behavioural determinants.

From the viewpoint of the behavioural scientist, these similarities extend the generality of the methods and principles of the behavioural analysis. Thus the experimental analysis of drug-taking may provide information of general value in the study of behaviour. More specifically, however, it is hoped that continued investigation of the conditions which produce, maintain, and alter drug-taking in experimental situations will lead to the availability of ways to control or eliminate similar behaviour in humans.

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A Semantic Aspect of Alcoholism

Nancy K. Mello¹

INTRODUCTION

Alcoholism has long been associated with the concepts of “need” and “craving” which are frequently advanced to account for addictive drinking. “Craving” has been defined as a “loss of control” over drinking and it implies that “every time the subject starts drinking, he is compelled to continue until he reaches a state of severe intoxication” (Mardones, 1963, p. 146). The circularity inherent in this reasoning is evident, *i.e.* the concepts of “need” and “craving” are defined by the behavior that they are invoked to explain. Moreover, the lack of experimental data about drinking patterns in alcoholics has contributed to an implicit reification of these concepts (*cf.* Mello, 1972).

One purpose of this paper is to reexamine the usefulness of the concept of “craving” in the context of some recent experimental findings. The development of the craving concept and some empirical results relevant to this construct, will be discussed. This review is also intended to provide a basis for reevaluation of the contribution of the notion of craving to current therapeutic strategies. The concept of craving appears to have acquired the status of dogma despite the absence of stringent empirical confirmation, and consequently has tended to limit the flexibility of treatment approaches to the disease of alcoholism.

¹Chief, Laboratory of Alcohol Research National Institute on Alcohol Abuse and Alcoholism ADAMHA, Washington, D.C. Now at Alcohol and Drug Abuse Research Center, Harvard Medical School, McLean Hospital, Belmont, Mass.

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Development of the "Craving" Concept

The notion that craving is a determinant of alcoholism has had a long, if not illustrious history. According to one reviewer, the oldest reference to alcohol craving in the medical literature appeared in 1819, and subsequently, in 1870 and 1880, craving was associated with alcohol withdrawal (Bensoussan, 1956). Although some writers have made an effort to distinguish between a type of craving which occurs as a function of withdrawal signs and symptoms and a general craving for alcohol, the basic notion appears to be essentially the same. Efforts to define the conditions under which the phenomenon is purported to occur have been rather superficial.

In a recent scholarly review on this topic, Keller (1972) has traced the development of the "loss of control" concept through its adoption by Alcoholics Anonymous and its enduring formal statement by Jellinek. According to Jellinek's original formulation

Loss of control means that as soon as a small quantity of alcohol enters the organism, a demand for more alcohol is set up which is felt as a physical demand by the drinker, . . . the 'loss of control' is effective after the individual has started drinking, but it does not give rise to the beginning of a new drinking bout (Jellinek, 1952).

Jellinek argues that the occurrence of voluntary abstinence indicates that the alcoholic can control whether or not he will drink on any occasion. Keller (1972) disputes this view and contends the "loss of control" does extend to initiation of a drinking spree and that this is in fact the essential aspect or pathognomonic sign of the illness. In his view, the symptom of loss of control appears only inconsistently as do symptoms of other diseases. Keller argues eloquently that the notion of alcoholics without loss of control "can cause confusion in the public mind, loss of confidence on the part of the patients, erroneous jurisprudence, and misdirection of effort by government agencies" (Keller, 1972, p. 163).

A number of other writers have also equated some variant of craving with alcoholism per se. Marconi (1967) has attempted to differentiate between "intermittent alcoholism" characterized by an inability to stop drinking and "inveterate alcoholism" characterized by an inability to abstain from drinking.

Usually, the term craving is used in an attempt to account for the perpetuation of drinking following the ingestion of *some* alcohol by an alcoholic. Originally, the term craving was not intended to account for the resumption of drinking following a period of sobriety. Isbell (1955) clearly argued that resumption of drinking cannot be explained by an acquired physical craving any more than can the initial excessive drinking which must precede the development of physical dependence. Although this distinction was emphasized by the WHO Expert Committee on Mental Health and Alcoholism in 1955, it has tended to become somewhat blurred in common practice and "craving" is often used to explain relapse after abstinence as well as compulsive drinking or drinking to postpone or to diminish withdrawal signs and symptoms. However, the alcohol addict may invoke alcohol craving as a reason for resumption of drinking with less frequency and enthusiasm than the attending clinician. A questionnaire follow-up study of 161 alcoholics who resumed drinking after treatment showed that only one per cent attributed drinking to "craving" (Ludwig, 1972). Psychological distress was the most frequent explanation offered (25%), followed closely by "no special reason," family problems and the pleasurable effects of alcohol.

Through the years of concern with alcohol craving, a curious range of explanations has been suggested to account for its presumed psychological or biological bases. The notion of an inherent or induced biochemical predisposition has gradually been replaced by learning theory concepts which argue that the stimulus of alcohol elicits a sequence of compulsive drinking. A recent sophisticated description of craving suggests that it "represents the cognitive correlate of a subclinical conditioned withdrawal syndrome and is likely to be evoked subsequent to any state of physiological arousal resembling this syndrome" (Ludwig and Wikler, 1974). Glatt (1967) has suggested that there may be an individual threshold, defined in terms of a critical blood alcohol level, beyond which some alcoholics are more likely to resume compulsive drinking. At another end of the continuum, it has been suggested that craving for alcohol "may be due not so much to a desire for the drinks themselves as to an instinctive dislike for inorganic water" (Cooke, 1936, p. 183) which, the author argues is not naturally suited to the human organism. Treatment of alcoholism with fruit juices, milk, whey and buttermilk is recommended (Cook, 1936). The assumption that excessive alcohol intake is somehow related to a "misinterpretation of natural thirst" recurs with some frequency (*cf.* Baldie, 1931; Silkworth and Texon, 1950).

It is apparent from the foregoing that there has been a continuing concern with the concepts of alcohol "craving" and "loss of control" over drinking. These notions are inextricably related to conceptualizations of the definition of alcoholism and polemics over its eligibility for classification as a disease. Although these concepts are presented with increasingly sophisticated elaborations which parallel the conceptual advances in psychiatry and reflect the verbal facility of the writers, there has been little change in the fundamental ideas involved. The conditions under which craving is purported to occur are seldom specified and its existence is inferred post-hoc from the occurrence of a drinking spree. Consequently, the essential confusion between factors which may contribute to the initiation of a drinking spree, and factors which may contribute to the maintenance of a drinking spree persists.

Some Implications of the "Craving Concept"

Perhaps the most important consequence of a general acceptance of the validity of the notion of craving has been the unquestioned adoption of a therapeutic goal of total abstinence for the alcoholic patient. It has often been assumed by the therapist, and by the alcoholic as well, that exposure to alcohol will trigger a sequence of uncontrolled drinking and intoxication, eventuating in stupor. It has been generally accepted that once the alcoholic is exposed to alcohol, he or she is thereby rendered totally incapable of exercising any control over drinking. Until very recently, there has been virtually no acknowledgement in the alcoholism literature of individual differences in the potential capacity for controlled drinking. The rigid taboo on any alcohol use deriving from the craving notion has formed an integral part of the therapeutic philosophy of many medical and paramedical therapists and of many voluntary agencies for assisting alcoholic patients such as Alcoholics Anonymous.

EXPERIMENTS RELEVANT TO THE CONCEPT OF "CRAVING"

The empirical evidence relevant to the construct of "craving" can be divided into three

general categories: (a) self-report material from alcoholic subjects, (b) direct behavioral observations of alcoholic subjects while drinking, and (c) clinical observations of the effects of social drinking on alcoholic patients. The following sections will consider these data in that sequence.

Self-Report Data

It has been generally acknowledged that the sober alcoholic tends to be a most unreliable informant. The adequacy of his description of a drinking experience may suffer from his inability to recall the details of that experience or from his attempt to anticipate the expectancies of the interviewer. Yet, most of our information about an alcoholic's drinking patterns and behavior during a drinking episode have come from his retrospective reports during sobriety. In fact the concepts of "craving" or "loss of control" have been elaborated primarily from anecdotal self-report material. Stein and co-workers (1968) have attempted to systematize such information by developing a questionnaire to distinguish "loss of control" drinkers from controlled drinkers on the basis of empirical item selection.

A sincere belief in the concept of craving could have both a decided psychological advantage and a disadvantage for the alcoholic individual. Acceptance of the notion of craving in effect excuses the alcoholic from any responsibility for his drinking behavior after he has consumed the first drink. The utility of appealing to such a concept for the alcoholic when confronted with an irate and disapproving family or a disappointed and frustrated therapist is all too obvious. The extent to which an unquestioned acceptance of the reality of craving may in turn become a subtle determinant of the alcoholic's drinking behavior is difficult to examine. However, the facile excuse may become the basis for a superstitious fear. Once an alcoholic begins to drink, he might cope with his fears of the inevitability of loss of control by perpetuating drinking to the point that his fears are realized. In other words, an alcoholic who is convinced that the inevitable consequence of the initiation of a drinking experience is loss of control, may feel compelled to enact the consequences quite independently of any biologically determined compulsion to do so.

Two investigators have asked alcoholics about their craving for alcohol in an experimental situation either before (Davis, 1971) or after (Merry, 1966) alcohol was provided. In contrast to the anecdotal self-report data, neither investigator found verbal acknowledgement of craving associated with the anticipation or consumption of alcohol. There were no differences in "craving intensity" scores when nine alcoholic subjects were given an orange-flavored mixture containing one ounce of vodka and when they received the orange-flavored mixture alone (Merry, 1966). These two mixtures were given after an overnight fast, in alternate two-day sequences over a period of 18 days. Craving intensity scores were even lower when two ounces of vodka were administered, even though each subject did report some craving (Merry, 1966).

In a second study, ten alcohol addicts were given low (16 oz.) or high (26 oz.) doses of alcohol in divided portions, once every four hours around the clock for five consecutive days (Davis, 1971). A variety of behavioral and physiological measures were made on these subjects and several dimensions of affective state and craving for alcohol

were assessed by a self report Q-sort technique. No subject indicated "craving" for alcohol using this technique. During the low dosage phase of each study, clinical interviews with patients indicated that they would prefer to be drinking a larger amount of alcohol than was being provided (Davis, 1971). However, preference for large amounts of alcohol and compulsive craving for the next drink are clearly very different dimensions of a drinking pattern. These data are consistent with the retrospective self-report study previously described in which craving did not appear to be relevant to resumption of drinking by 161 alcohol addicts (Ludwig, 1972).

Ludwig and Wikler (1974) have subsequently reported that 78 per cent of a sample of 60 alcoholics report "craving" and 61 per cent report increased craving after one or two drinks. The authors argue that any reason an alcoholic offers to justify an initial relapse to alcohol abuse "is probably a reflection of underlying craving which, in turn, is an automatic concomitant of a subclinical conditioned withdrawal state or related state of physiological arousal" (Ludwig and Wikler, 1974). In the opinion of this reviewer, arguments of this sort, no matter how cogently presented, are seriously limited by their total reliance on hypothetical intervening variables which cannot be directly observed. Examination of the validity of the construct of craving can best be accomplished through the observation of an alcoholic's behavior. Since verbal behavior is often an unreliable measure, observation of drinking behavior would seem to offer the most powerful test of the craving hypothesis. For example, if alcoholics were observed to consistently drink compulsively to a state of severe intoxication after consuming small amounts of alcohol, this would provide empirical confirmation of the basic craving hypothesis. If such drinking behavior were accompanied by verbal descriptions concordant with the notion of craving, this would strongly support the adequacy of the concept as a descriptive convenience. However, in fact, there has been a dramatic absence of such confirmatory behavioral data.

Direct Observations of Drinking Behavior

There have been a number of studies in which subjects have been allowed to work at a simple task to earn up to 32 ounces of alcohol per day (Mello and Mendelson, 1965; Mendelson and Mello, 1966; Mendelson *et al.*, 1968; Mello *et al.*, 1968; Mello and Mendelson, 1972; Mello, 1973a; Nathan *et al.*, 1970a, b, 1971, 1972), or to drink up to 32 ounces of alcohol per day without work (Mello and Mendelson, 1970, 1972). The craving hypotheses would predict that alcoholics confronted with an opportunity to drink large amounts of alcohol would rapidly drink to a point of severe inebriation and stupor. In actual fact, no alcoholic subject allowed to freely program his drinking has shown a "loss of control" of drinking or a tendency to "drink to oblivion" (Mello and Mendelson, 1965; Mendelson and Mello, 1966; Mendelson *et al.*, 1968; Mello *et al.*, 1968; Mello and Mendelson, 1970, 1972; Mello, 1973; Nathan *et al.*, 1970a and b, 1971, 1972).

In most of the studies in which subjects performed a simple operant task to earn their alcohol, the tasks were sufficiently simple that subjects could earn alcohol irrespective of their intoxication level (*cf.* Mello and Mendelson, 1965; Mendelson *et al.*, 1968; Mello *et al.*, 1968; Mello and Mendelson, 1972; Nathan *et al.*, 1970a, b, 1971, 1972). Consequently, the failure to drink to achieve a "state of oblivion" cannot be attributed to an *inability to perform* successfully a complex discrimination task and thereby acquire more alcohol. In fact, the alcoholic subjects that we have observed have shown a striking

*behavioral tolerance*² for alcohol. Our subjects have continued to perform quite complex operant vigilance tasks and delayed matching-to-sample tasks with a surprising degree of accuracy even at blood alcohol levels in excess of 250 mg/100 ml (Mello *et al.*, 1968; Mello, 1973a).

No subject allowed to determine his own volume and frequency of alcohol intake has shown a loss of control of drinking, and no subject given an opportunity to drink 32 ounces of alcohol per day has consumed all the alcohol available within a 15-day drinking period. No subject drank all the alcohol available, even though his drinking did not involve the performance of any operant task (Mello and Mendelson, 1970, 1971). Subjects rarely drank in a pattern that maintained stable blood alcohol levels in either a work-contingent or a spontaneous drinking situation (Mello and Mendelson, 1972).

There are a number of instances in which alcoholics have been shown to be able to exercise considerable control over their drinking behavior in an experimental ward context. Several investigators have observed that the amount of alcohol an alcoholic will consume is a function of the *amount of work* (performance on an operant task) required to obtain the alcohol (Mello *et al.*, 1968; Mello and Mendelson, 1972; cf. Mello 1972 for a review). For example, subjects required to make 16 consecutive correct responses on a simple vigilance task to earn 10 ml of bourbon, averaged blood alcohol levels that were twice as high as alcoholic subjects required to make 32 consecutive correct responses on the same vigilance task (Mello *et al.*, 1968). In other words, those subjects who were required to work half as much for their alcohol drank twice as much as a comparable group of subjects in the same situation. The observation that the volume of alcohol consumed by an alcoholic can be manipulated by the amount of work required to obtain it argues strongly against the general applicability of the concept of craving. Further evidence of an alcoholic's capacity to control his drinking was the finding that subjects in the 16 and 32 consecutive response requirement groups tended to work for comparable amounts of alcohol in a single session. Most subjects tended to earn between one and two and one-half ounces before drinking (Mello *et al.*, 1968) and this volume preference has been confirmed repeatedly (Mello and Mendelson, 1971).

In a subsequent study, when the task required was to press a simple button box for points to obtain alcohol, alcoholics showed a dramatic dissociation between periods of working for alcohol and cigarettes and periods of alcohol consumption. Subjects rarely worked while they were drinking and all maintained a pattern of discrete working-drinking intervals over two months. This dissociation was surprising, since the task was not at all demanding and one ounce of alcohol could be earned in about five minutes of steady, rapid performance (Mello and Mendelson, 1972). The fact that drinking episodes were not sustained indicates voluntary control over drinking. A comparable pattern of work-contingent drinking and abstinence has also been observed by Nathan *et al.* (1970a, 1971, 1972).

These studies suggest that motivation for alcohol is a complex interaction of the availability of, and the effort required to obtain, alcohol. The observation that an alcoholic's alcohol intake can be modified by the cost contingencies in an experimental

² Efforts to evaluate the significance of amounts of alcohol consumed by alcoholics often ignore the importance of behavioral tolerance which characterizes this addictive disorder. The alcoholic may be able to function well and perform complex behavioral tasks at high blood alcohol levels between 150 and 250 mg/100 ml. Despite the ingestion of large amounts of alcohol, the tolerant addict may not appear to be intoxicated. A non-addicted social drinker would be unable to function at the blood alcohol levels achieved by tolerant addicts (cf. Mello, 1973a; Mello and Mendelson, 1974a). However, the specious and circular argument is sometimes made that sustained high blood alcohol levels in alcoholics indicate the existence of "craving."

situation has implications for *therapeutic* management. It is reasonable to assume that an alcoholic could learn to control his drinking under certain conditions. It is curious that the somewhat trivial cost-effort contingency in these experiments did affect drinking behavior since the cost consequences of alcoholism in real life usually fail to modify drinking except on a transitory basis. However, there are considerable data to demonstrate that the efficacy of a rewarding or a punishing event and the subsequent control of behavior is a function of temporal proximity of the consequence to the behavior (cf. Mills *et al.*, 1971). Therefore, an expenditure of 15 minutes as opposed to 30 minutes of effort for one drink may be more effective in controlling alcohol intake than the repeated threats of job loss or home loss over months or years. A better quantification of this issue would require study of drinking behavior modification in a therapeutic token economy, something like the token economy for alcoholics explored by Narrol (1967).

Perhaps even more compelling than the effect of cost on alcohol intake is the finding that it is possible to buy abstinence from alcoholic subjects (Cohen *et al.*, 1971a, b). An interesting corollary of the question, "How much is an alcoholic willing to work for alcohol?" is "How much will it cost to keep an alcoholic from drinking?" Cohen and her associates (1971a, b) have attempted to pose this question to alcoholic volunteers living on a research ward for 50 and 60 days.

In the context of a token economy, it was possible to buy abstinence in two alcohol addicts for periods up to seven days. During the baseline period, a titrating schedule of payments for abstinence was used to determine the "abstinence purchase threshold" for each subject (*i.e.* \$7.00 and \$12.00 respectively). The investigators then attempted to determine if abstinence so established could be disrupted either by a delay in payment or consumption of a priming dose of alcohol (zero to 10 ounces in three hours).

These subjects were able to tolerate up to a one-week delay in payment, but abstinence was disrupted by two to three weeks delay. Ingestion of over six ounces of alcohol also disrupted abstinence; however, the effects of both types of disruption could be reversed by increasing the amount of abstinence payments. Some inference can be made about the relative disruptive potency of delay of payment and alcohol by comparing the subsequent costs of abstinence. After a priming dose of alcohol, only \$3.00 was required to reestablish abstinence, whereas any delay in payment exceeding one week required a \$7.00 or \$10.00 increase over the baseline payment rate (Cohen *et al.*, 1971a, b). These data are clearly inconsistent with the concept of craving.

Finally, a craving notion would predict that an alcoholic given free access to alcohol would continue to drink for as long as that resource remained available and/or his physical health permitted. However, it has been consistently observed that subjects allowed to drink alcohol continuously over long periods of 30 to 60 days, spontaneously *initiate* and *terminate* several drinking episodes. No research subject has consumed high doses of alcohol for more than 20 *consecutive* days in the experience of most investigators (Mendelson *et al.*, 1968; Mello and Mendelson, 1970, 1972; Nathan *et al.*, 1970a, b, 1971). Moreover, it has been repeatedly demonstrated that the availability of alcohol alone is not sufficient to maintain long-term drinking. There have been several examples of subjects who voluntarily stopped drinking when a partner was no longer available or in response to a stressful event (Mendelson *et al.*, 1968; Mendelson and Mello, 1966).

One further indication of the control that alcoholics are able to exercise over their drinking behavior, even after a prolonged drinking episode, is that many deliberately taper their drinking in an effort to avoid the severe consequences of abrupt alcohol withdrawal. Such deliberate tapering of alcohol intake has been frequently observed by a

number of investigators (Mello *et al.*, 1968; Mello and Mendelson, 1970, 1972; Nathan *et al.* 1970 a, b, 1971).

One of the most compelling examples of the capacity for controlled drinking behavior has been supplied by the work of Gottheil *et al.* (1971, 1972a, b). For four weeks of a six-week treatment program, alcoholic patients were allowed to choose to drink one ounce of alcohol, two ounces or nothing each hour, on the hour. This schedule yields 13 decision points per day and a maximum of 26 ounces in the alcohol available period (9:00 a.m. to 9:00 p.m.). In a sample of 29 patients studied, two left the program and one-third elected not to drink, one-third began drinking and stopped during the course of the program and the remainder drank heavily. Representative case histories of patients who were able to stop drinking are presented in Gottheil *et al.*, (1973).

The fixed interval drinking decision procedure devised by Gottheil and co-workers is an interesting approach to teaching the alcoholic something about his own capacity to control his drinking behavior (Gottheil *et al.*, 1971, 1972a; Gottheil, 1973). These basic findings were reconfirmed and extended in a second study of 25 patients in which nine did not drink in the presence of drinking others; nine others stopped drinking by the third week; three patients drank sporadically and only four drank heavily and consistently. However, six-month self-report follow-up data indicated that controlled drinking in the research setting did not necessarily predict moderate drinking at home (Gottheil *et al.*, 1972b).

Cohen *et al.* (1971a, c; 1972) have found that moderate drinking (5 oz. per day) can be maintained in alcoholic subjects for 5 successive days by manipulating conditions of the total living environment as reinforcers. If subjects drank moderately, their environment was "enriched," *i.e.* paid work opportunities, recreational activities, phone calls, reading materials, standard diet and a bedside chair were all available. If subjects failed to drink moderately, they were placed in an "impoverished" environment with pureed food and removal of all the other privileges. Subjects were observed for five consecutive weeks in which environmental contingencies were alternated with an impoverished environment period during which all subjects drank 8 to 24 oz. of alcohol per day. In a subsequent study, environmental contingencies were alternated with periods of exposure to an enriched environment. In each study, subjects drank moderately only when the environmental contingencies were in effect.

Paredes and co-workers (1973) have also presented evidence that social conditions can facilitate controlled drinking. Groups of 12 alcoholics lived for five weeks on a hospital ward with chronic schizophrenic patients. After two weeks, each of 27 subjects was given alcohol over a 9½ hour period on each of two consecutive days. Only one of a group of 12 was given alcohol at any one time and a maximum blood alcohol level of 140 mg/100 ml was imposed. Since subjects initiated and stopped drinking upon request, then remained voluntarily in the hospital, the investigators interpreted these data as inconsistent with the loss of control hypothesis (Paredes *et al.*, 1973).

Evidence of controlled drinking has also been reported in a study of the effects of acute rather than chronic alcohol administration. Marlatt and co-workers (1973) examined the effect of accurate vs. inaccurate information about the alcohol content of a beverage on drinking behavior in alcoholic subjects and social drinkers. The drinking rates of both groups were not significantly affected by the presence or absence of alcohol (5 oz.). The subjects' expectancy about the beverage content rather than the beverage content per se appeared to determine the total amount consumed, the amount consumed per sip and the rate of drinking. Although alcoholics who expected alcohol did drink more

than controls, there was no indication of "loss of control" over drinking. Drinking rates tended to decrease for both groups of subjects over the experimental session (Marlatt *et al.*, 1973). Marconi *et al.* (1967) compared the volume of alcohol consumed by a group of "intermittent" and "inveterate" alcoholic subjects. The "intermittent" group drank an average of 0.19 gm/kg more than the "inveterate" group, and the investigators argued that this demonstrates "an inability to stop." These data are somewhat difficult to evaluate since degree of intoxication and blood alcohol data are not presented. However, it appears that only three of the 13 subjects drank the maximum amount of alcohol available (0.5 gm/kg).

Clinical Observations of Social Drinking in Alcoholics

There have been an increasing number of clinical reports indicating that some former alcoholics can drink socially and function well for continuous periods of two and one-half to eleven years (Davies, 1962; Pattison *et al.*, 1968; Bailey and Stewart, 1967; Gerard and Saenger, 1966). A number of investigators have reported better overall adjustment and social functioning in alcoholics who drink moderately than in ex-alcoholic abstainers. The relevant studies have been critically reviewed by Pattison (1966, 1968) and will not be repeated here.

The adequacy of a criterion of abstinence to define successful treatment of alcoholism has been repeatedly challenged by Pattison and his associates (1966, 1968). Pattison (1966) points out that alcohol abstinence may not reflect personality reintegration, but rather may require continued "treatment" for its maintenance. Moreover, Pattison (1966) reviews the evidence that neither duration nor success of therapy is necessarily related to abstinence during treatment. The notion that moderate drinking may facilitate adjustment in some patients is a striking departure from the traditional approach to therapeutic management.

A second change in attitudes towards treatment is a slowly developing acceptance of the notion that alcohol may be a useful adjunct to the psychotherapeutic process. It was once generally agreed that treatment of the alcoholic should only be conducted if the patient was sober. There is now increasing consideration of the view that it may be ineffective or impossible to treat alcoholism if the symptom of drinking is eliminated and situational constraints are imposed such that the symptom is unlikely to recur (Cantor, 1968). Among the advantages of attempting psychotherapy with a mildly intoxicated patient are a greater expressiveness by the patient and a more realistic view of the effects of alcohol for the therapist. Diethelm and Barr (1962) interviewed acutely intoxicated alcoholic patients and found that patients expressed emotions, especially hostility and guilt, which they had not expressed during sobriety. Usually these patients forgot the content of the interview once they became sober again.

Clinically, the dissociative effect of alcohol is most often expressed by a failure to recall aversive consequences of drinking (e.g. depression, anxiety, illness) during a subsequent period of sobriety. Alcoholics tend to form positive expectancies about a forthcoming drinking experience, and following a period of chronic intoxication, they tend to recall their experience in terms of the pre-drinking expectancy, rather than the events that actually transpired (McGuire *et al.*, 1966; McNamee *et al.*, 1968; Tamerin *et al.*, 1970). The prevalence of these dissociative phenomena would seem to indicate the desirability of a therapeutic approach directed towards assisting patients to integrate

feelings expressed during intoxication with self-perception during sobriety (cf. Paredes *et al.*, 1971; Mello and Mendelson, 1974a; Mello, 1972). There is some evidence that giving alcohol to alcoholics in an experimental, quasi-therapeutic situation is not damaging and may even be beneficial (Faillace *et al.*, 1972).

POTENTIAL RE-ADDICTION: A FACTOR IN SOCIAL DRINKING?

Another issue which is relevant to the question of social drinking by alcoholics is their potential for re-addiction as compared with problem drinkers; *i.e.* the rapid development of tolerance and subsequent abstinence signs and symptoms upon cessation of drinking.

There are few experimental data now available to clarify the nature of the addictive process and the determinants of "re-addiction." The duration of the "memory for addiction" in a drug abstinent subject has been shown to extend up to 12 months in narcotics addicts (Martin and Jasinski, 1969). Unsystematic observations of alcoholics testify to the occurrence of severe abstinence signs and symptoms on abrupt termination of a brief drinking period, even after prolonged alcohol abstinence due to incarceration for public drunkenness from one to 6 months periods (cf. Taylor, 1966). Often these alcohol addicts had only four or five brief opportunities to drink each year since the remainder of their time was spent in a "correctional" institution. Yet it appeared that these few drinking episodes were sufficient to sustain or re-induce physical dependence as manifest by withdrawal signs and symptoms. Consequently, the fact that the alcoholic is vulnerable to re-addiction upon re-exposure to the agent is one constraint on social drinking. It should be noted that these observations were made prior to the *Easter v District of Columbia*, *Driver v Hinnant* (1966) and *Powell v Texas* (1968) decisions.

The expression of withdrawal signs and symptoms in man requires an as yet undetermined time, dose and pattern of alcohol consumption (cf. Mello and Mendelson, 1970, 1974b). Since the alcohol addict apparently maintains some residual tolerance for alcohol after a period of abstinence, he may require progressively more alcohol to produce a change in feeling state. Adequate techniques to assess such residual tolerance for alcohol have not been developed. As Cochin and Kornetsky (1964) have pointed out the assessment of the rate of disappearance of tolerance is necessarily confounded since the procedures used to test for tolerance appear to perpetuate the phenomenon.

The extent to which alcohol addiction is biologically and behaviorally comparable to narcotics addiction has been the subject of considerable unresolved speculation. A loss of tolerance following drug withdrawal in narcotic addicts has been well documented and addicts may undergo withdrawal voluntarily to reduce the amount of drug that they require each day (Goldstein *et al.*, 1968). However, there are data which attest to the long-term (3-6 months) effects of chronic narcotics addiction (Goldberg and Schuster, 1969; Himmelsbach, 1942; Fraser and Isbell, 1952; Martin *et al.*, 1963; Sloan and Eisenman, 1968) and even of acute doses of morphine (Cochin and Kornetsky, 1964; Kornetsky and Bain, 1968). Since there is as yet no specific pharmacological antagonist for alcohol, comparable to nalorphene, naloxone, cyclazocine or naltrexone for opiate narcotics, rapid assessment of the degree of physical dependence following various alcohol administration schedules has not been possible.

The implicit assumption that physical dependence is one aspect of an addict's motivation for the drug is a complex and difficult issue to approach experimentally (cf. discussions by Wikler, 1967; Jaffe, 1968). Initiation of a re-addictive sequence by a

withdrawn addict is probably the complex resultant of a number of psychogenic and stress response factors. For the ex-morphine addict, re-exposure to morphine is a euphoria-inducing experience, whereas for the nonaddict, morphine produces dysphoria (Wikler, 1961). An examination of the *initial* effects of alcohol on mood in alcoholics showed great inter and intra subject variability (Davis, 1971). An anticipatory depression was seen frequently and a brief euphoria did not appear to persist with prolonged drinking and high doses of alcohol. In contrast to the euphoric effect usually produced in normal drinkers, alcohol produces a progressive dysphoria in alcoholics (cf. Mendelson, 1964; McNamee *et al.*, 1968; Mello, 1972 for review).

Once an addictive drug consumption pattern has been reestablished, the role of physical dependence in maintaining that pattern is less clear for the alcoholic than for the narcotics user. If avoidance of withdrawal signs were the factor which motivates an alcoholic to continue drinking, it would be expected that during a drinking spree, he should consistently drink enough to avoid partial withdrawal signs and symptoms. Moreover, he should consistently taper his drinking when forced to stop by an external constraint. However, we have observed that alcoholics frequently experience partial withdrawal signs during a drinking episode. Despite the attendant discomfort, the alcoholic does not invariably respond to incipient withdrawal signs by increasing his drinking. On some occasions, these partial withdrawal signs have persisted for 3 or 4 days, modulated by a minimal intake of alcohol (Mello and Mendelson, 1970, 1972). This situation may resemble that of the narcotics addict in which incipient withdrawal signs appear to add to both the gratification and perpetuation of drug use (Wikler, 1961). Wikler has observed that although "the intensity of the initial 'euphoria' is not regained as long as the uninterrupted schedule of drug administration is maintained" drug use may come to produce another sort of pleasure, "namely that arising from the relief of such abstinence discomfort as developed toward the end of intervals between injections" (Wikler, 1961, p. 75).

One promising approach to the question of the role of physical dependence in maintaining drug administration is to determine the reinforcing properties of small doses of drugs within an operant conditioning framework. Reviews of experiments on alcohol (Woods *et al.*, 1971) and opiates (Woods and Schuster, 1970) indicate that monkeys will respond to self-administered intravenous doses of these drugs at levels *below* that required to produce physical dependence. It is well established that monkeys that are physically dependent will respond for narcotics, presumably to avoid withdrawal signs (Woods and Schuster, 1970). The extent to which the reinforcing properties of a drug may be enhanced following withdrawal from the drug has yet to be determined (see also Mello, 1973b for discussion).

CONCLUSIONS

Although the assembled evidence seems to demonstrate that "craving" is a logically and an empirically inadequate explanatory concept to account for addictive drinking, my intention has *not* been to argue by implication that moderate drinking is the best therapeutic goal for *all* alcoholics. Rather, the clinical and behavioral data which are inconsistent with a "craving" hypothesis have been presented in an effort to modify the constraining influence of this usually unquestioned concept and to facilitate a reexamination of appropriate treatment goals for individual alcoholics.

Insofar as the "craving" myth may have been perpetuated by ambiguities in diag-

nostic criteria for alcoholism, the recent formulation by the National Council on Alcoholism represents an important conceptual advance (1972). The National Council on Alcoholism has suggested criteria to help the physician identify the medical and physiological concomitants of alcoholism. The behavioral and attitudinal accompaniments of this complex disorder are also described. It is significant that "loss of control over drinking" is not considered an adequate criterion for the differential diagnosis of alcoholism, since it is subjective and inferred and cannot be objectively verified.

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An Objective Look at Three Behavioral Treatment Approaches to Alcoholism

Peter E. Nathan¹, G. Terence Wilson,
John J. Steffen, Stanley J. Silverstein

INTRODUCTION

During the past ten years, excessive drinking by alcoholics has become a prime target of the efforts of behavior modifiers. A number of converging factors appear to have been responsible for this current trend. Firstly, alcoholism is one of the country's major public health problems. Secondly, many nonbehavioral mental health workers recognize the relative ineffectiveness of their procedures with alcoholics. A third factor is that productive early basic research on alcoholism was undertaken by behaviorally oriented researchers; and fourthly, the disorder called alcoholism is defined by a single quantifiable target behavior whose modification would represent undoubted behavioral success.

Originally, behaviorally trained clinicians designed treatment strategies whose final therapeutic aim was abstinence. There were several reasons for this. One was the widespread belief (instilled by Alcoholics Anonymous in every new recruit) in the "one drink, one drunk" premise. Another such belief was that alcoholism is the consequence of an inevitable loss of control set off by the reintroduction of alcohol into a physiological system which inevitably reacts violently, maladaptively, and in an uncontrolled fashion to its introduction. Another reason to aim for abstinence was the widespread acceptance of the validity of the anxiety reduction model of alcohol addiction, whereby cessation of drinking would eliminate the reinforcing consequences of drinking. Though recent research has brought into question each of these assumptions in turn (e.g., Mello, 1972; Nathan and O'Brien, 1971; Okulitch and Marlatt, 1972), behaviorally oriented clinicians have reported numerous examples of the use of electrical aversion (Blake, 1965, 1967; MacCulloch, Feldman, Orford, and MacCulloch, 1966; Miller and Hersen, 1972; Vogler, Lunde, Johnson, and Martin, 1970, 1971) and chemical aversion (Lemere and Voegtlin,

¹ The Psychological Clinic, Rutgers University, New Brunswick, New Jersey 08903

1950; Raymond, 1964; Sanderson, Campbell, and Laverty, 1962, 1963), sometimes in isolation, sometimes in conjunction with other behavioral procedures, in the effort to bring about temporary or permanent abstinence by alcoholics. Though other behavioral methods, including covert sensitization (Ashem and Donner, 1968; Cautela, 1967), systematic desensitization (Kraft, 1969; Kraft and Al-Issa, 1967), and broad-spectrum behavior therapy (Lazarus, 1965) have also been employed with alcoholics, electrical and chemical aversion have been most widely employed in this regard, despite the continuing controversy which surrounds their efficacy (Franks, 1970; Nathan, 1974).

In response to this controversy about the efficacy of behavioral efforts to induce abstinence, to reports that some alcoholics have become social drinkers (Bolman, 1965; Davies, 1962; Pattison, 1968), and to data from controlled studies of the "loss of control" phenomenon which suggested that it is not an invariable accompaniment of chronic alcoholism (Cutter, Schwab, and Nathan, 1970; McNamee, Mello, and Mendelson, 1968; Williams, 1970), controlled drinking by alcoholics has recently emerged as a treatment goal for behaviorally oriented clinicians working with chronic alcoholics. Among the behavioral treatment methods employed in this context have been efforts to train alcoholics to discriminate their own blood alcohol levels and then use this new-found skill to moderate consequent drinking (Lovibond and Caddy, 1970), to give alcoholics training in social skills incompatible with immoderate drinking in a treatment paradigm that also included electrical aversion therapy for uncontrolled drinking (Mills, Sobell, and Shaefer, 1971; Sobell and Sobell, 1973), and to alter the environmental circumstances of alcoholics to enable them to attain stimulus control over their drinking behavior (Bigelow, Liebson, and Griffiths, 1973; Cohen, Liebson, Faillace, and Allen, 1971). Though behavioral efforts to induce controlled drinking by alcoholics continue apace, data from these early studies attesting to the permanency and generalization of controlled drinking attained during experimental treatment have not been completely convincing.

Each of the three controlled laboratory studies described in this chapter was designed to investigate one or more problems raised by a prior behavioral effort to induce abstinence or controlled drinking in alcoholic subjects. In each case the questions raised derived from design or control problems associated with the clinical application of behavioral methods whose parameters had not yet been fully explored.

All three studies were undertaken at the Alcohol Behavior Research Laboratory, Rutgers University. The subject area of the Laboratory is shown in Figure 1. The Laboratory is designed to permit continuous, 24-hour surveillance of behavior by direct observation from the Observation Room and indirect observation by closed-circuit audio and video systems.

STUDY 1: EXPERIMENTAL ANALYSIS OF ELECTRICAL AVERSION TO SUPPRESS DRINKING

A recent review of studies employing electrical aversion to treat alcoholics (Nathan, 1974) made the point that, despite its widespread use, electrical aversion does not constitute a definitive behavioral treatment for alcoholism. Specifically, that review agreed with Franks (1970), that electrical aversion methods whose sole aim is to punish drinking without also developing behaviors incompatible with drinking (e.g., enhanced social functioning, anxiety reduction) have not been proven effective. The review also cited the thoughtful paper by Wilson and Davison (1969) to the effect that consideration of the topography of the stimuli and responses most closely associated with drinking by alcoholics would lead to choice of more appropriate aversive consequences for drinking such

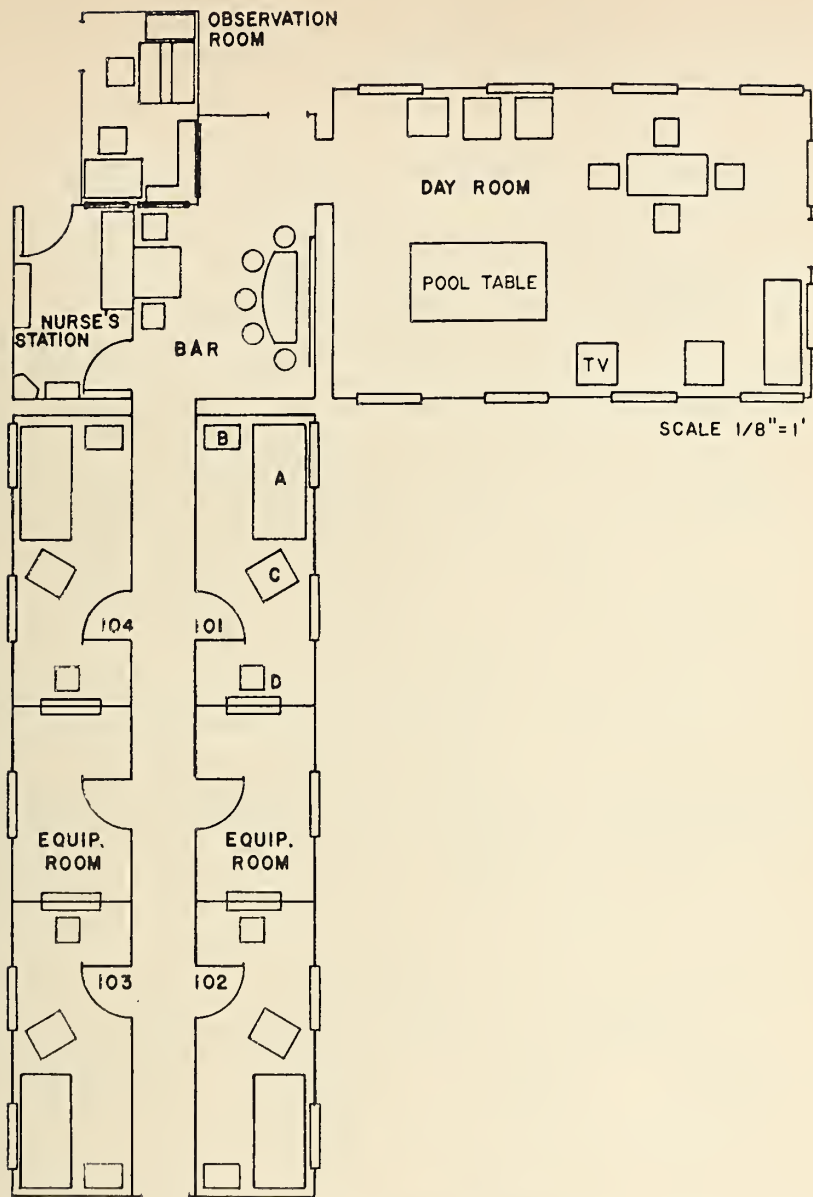


Figure 1. *Schema of the Alcohol Behavior Research Laboratory, Rutgers University.*

as chemical agents to induce nausea. Finally, the review pointed out that no prior clinical study of electrical aversion with alcoholics had compared immediate and longer-term effects of the procedure on drinking behavior, a design omission that bulked large in its unenthusiastic assessment of the overall efficacy of electrical aversion vis-à-vis alcoholics.

The program of research on electrical aversion described here was designed to explore the following matters: (1) effects on drinking of the "standard" escape conditioning method of electrical aversion, as recommended by Rachman and Teasdale (1969) and used by Blake (1965, 1967) and Vogler, Lande, Johnson, and Martin (1970, 1971); (2) the suppressant effects of an instrumental conditioning alternative to the "standard" method, in which each drink of alcohol is invariably followed by electric shock which cannot be escaped; (3) analysis of the determinants of the suppressant effects of the

alternative method; specifically, comparison of the suppressant effects of contingent versus noncontingent shock within that instrumental paradigm.

1) *Effects on Drinking of the "Standard" Method of Electrical Aversion.*

Six chronic alcoholic Ss, two in an initial 15-day study, four in a second 17-day study, participated in this research. All met a variety of selection criteria which ensured that they were chronic alcoholics in good physical and psychological health.

The two Ss in the first study were allowed *ad lib* alcohol up to a maximum of 18 ounces of 86-proof blended whiskey during each of three consecutive baseline days. The four Ss in the second study could drink up to 30 ounces a day during a similar three-day baseline period. Ss in the first study were then administered 30 trials of either aversive escape conditioning or backward conditioning on each of three succeeding days. Ss in the second study received 30 trials of either aversive escape conditioning or backward conditioning on each of four following days. Aversive escape conditioning, the method employed by both Blake (1965) and Vogler and his colleagues (1970), requires Ss first to take a sip of alcohol into their mouths, at which point they receive electric shock until they expectorate the alcohol. Backward conditioning in both studies involved administration of shock before ingestion of alcohol; the backward conditioning treatment was included as a control procedure for nonspecific treatment effects as well as for the specific effects of shock as an unconditioned stimulus. Reinstatement of the original baseline *ad lib* condition for three days then followed in both studies, after which the experimental procedures were reversed in a crossover design for, respectively, three and four days. A final return to *ad lib* drinking for three days completed the study.

TABLE I

MEAN NUMBER OF OUNCES OF ALCOHOL CONSUMED

	Baseline 1 (3 days)	Treatment 1 (3 days)	Baseline 2 (3 days)	Treatment 2 (3 days)	Baseline 3 (3 days)
Subject 1	10.7	Escape Conditioning	9.7	Backward Conditioning	10.3
Subject 2	11.0	Backward Conditioning	11.3	Escape Conditioning	11.7

Tables I and II show that neither aversive escape conditioning nor backward conditioning was effective in modifying Ss' alcohol intake, a result suggesting that the positive follow-up data both Blake and Vogler reported after comparable periods of aversive escape conditioning may well have been a function of other than the specifics of the conditioning method they employed.

TABLE II

MEAN NUMBER OF OUNCES OF ALCOHOL CONSUMED

	Baseline 1 (3 days)	Treatment 1 (4 days)	Baseline 2 (3 days)	Treatment 2 (4 days)	Baseline 3 (3 days)
Subject 1	21.3	Escape Conditioning	21.5	Backward Conditioning	23.0
Subject 2	13.7		15.0		15.5
Subject 3	28.0	Backward Conditioning	25.5	Escape Conditioning	1.5
Subject 4	24.3		25.5		26.5

2) Suppressant Effects of an Instrumental Conditioning Alternative to the "Standard" Aversive Escape Conditioning Method.

This study explored the suppressant effects of an instrumental conditioning method thought to be a possible alternative to the "standard" aversive escape conditioning method.

Four chronic alcoholic Ss, selected according to the same criteria used before, were permitted *ad lib* baseline drinking for two days up to a maximum of 30 ounces each day. All Ss then received experimenter-administered punishment training on a 100 per cent schedule such that ingestion of a one-ounce drink of beverage alcohol was followed immediately and invariably by a brief but painful electric shock. After a two-day return to baseline conditions, punishment was restored, at first on a 100 per cent (CRF) basis, then on a variable schedule. In all cases punishment during this treatment period was self-administered: Ss were told that shock would no longer be administered by an experimenter, as before, but that they would have to push the shock button themselves whenever they completed a drink. Though Ss observed that self-administration of shock was often extremely difficult, all did so whenever shock was required. A six-day baseline period and then a final three-day self-administered punishment period followed ten initial days of self-administered punishment.

Figure 2 shows that contingent shock, whether experimenter- or self-administered, suppressed drinking below baseline levels, even though the punishment schedule during the first self-administered shock period was made progressively more intermittent until it was faded out completely (during two days of an extinction schedule labeled EXT).

These data indicate, then, that this method of electrical aversion can be successful in suppressing drinking in chronic alcoholics in the laboratory, a finding which impels development of methods to extend the paradigm to the natural environment. Of greater relevance to this basic research program, though, is that because the design of this study did not permit reliable specification of the active suppressant agent in our instrumental method (e.g., contingent shock, placebo effects, time in study), another study was designed to enable this necessary specification.

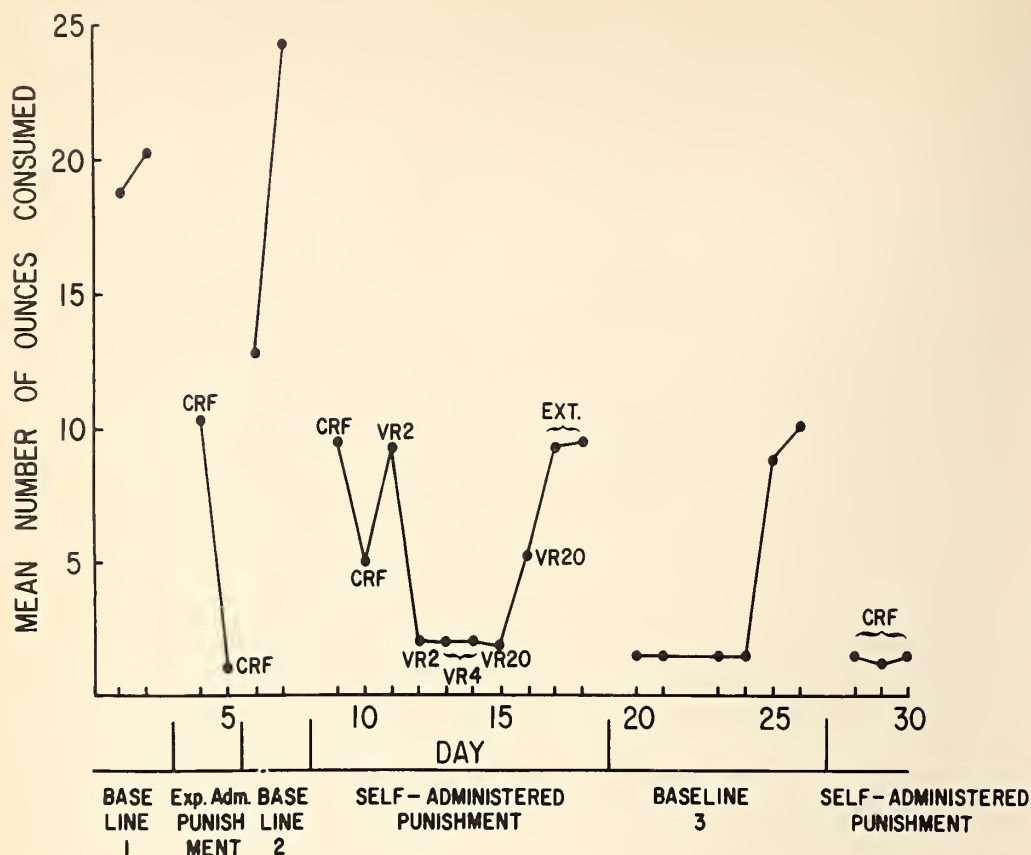


Figure 2. Mean number of ounces of beverage alcohol consumed by Study I subjects during successive baseline, experimenter-administered contingent punishment, and self-administered contingent punishment periods.

3) Suppressant Effects of Contingent Versus Noncontingent Shock in an Instrumental Conditioning Paradigm.

All four of the chronic alcoholic Ss who participated in this ten-day study were first permitted to drink up to 30 ounces of beverage alcohol a day on a *ad lib* basis during a two-day baseline period. Two of these Ss then received contingent shock during two succeeding days according to the method described above, while the other two "yoked" Ss received shock of equal frequency, intensity, and spacing on a noncontingent basis. After an intervening nondrinking day, experimental conditions were reversed, with those Ss who had received contingent shock now receiving noncontingent shock and *vice versa*. A two-day baseline period concluded the study.

Figure 3 shows that contingent shock effectively suppressed drinking by all Ss whether imposed first or second; conversely, the figure shows that noncontingent shock had little or no effect on drinking behavior regardless of the order in which it was imposed. These findings suggest, then, that shock imposed within this instrumental paradigm must be contingent upon actual drinking to be an effective suppressant of that behavior.

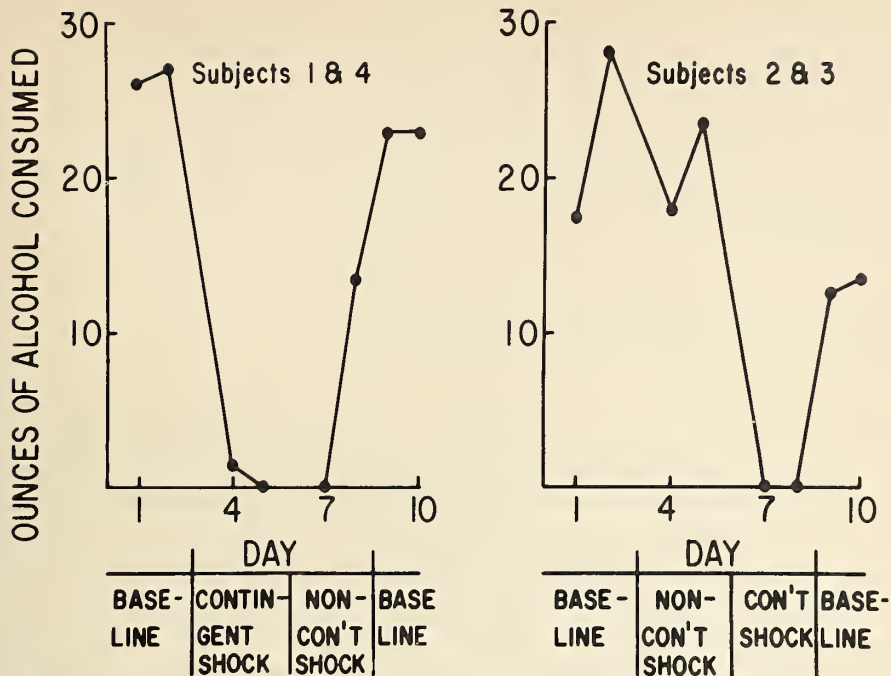


Figure 3. Mean number of ounces of beverage alcohol consumed by Study I subjects as a function of contingent and noncontingent shock.

While replication and extension of the four separate studies included within this research program must be undertaken, results thus far do suggest that there seem to be clear-cut differences in the abilities of the "standard" aversive escape paradigm and an alternative instrumental conditioning paradigm to modify patterns of drinking by alcoholics. Whether these differences will maintain on replication with different Ss in different laboratories and whether they bear a direct relationship to subsequent long-term drinking by chronic alcoholics remain, of course, to be determined.

STUDY II: TENSION REDUCTION AND DRINKING AFTER ELECTROMYOGRAPHIC FEEDBACK TRAINING

This study investigated the effects of alcohol upon muscle tension in four chronic alcoholics and, reciprocally, the effects of feedback-induced relaxation upon the drinking behavior of the same subjects. The study examined four principal questions:

Relationships between Muscle Tension Level and Blood Alcohol Level

Previous research on the tension reduction hypothesis of alcoholism etiology has focused on the assumption that alcohol reduces tension (Cappell and Herman, 1972; Conger, 1956). Most positive reports in this regard, however, studied the effects of alcohol upon infra-human organisms (Cappell and Herman, 1972). Recently, several studies investigating the effects of long-term alcohol consumption upon self-reported mood in alcoholics (Davis 1971; Mendelson, La Dou and Solomon, 1964; Nathan and O'Brien, 1971) failed to support the tension-reduction hypothesis, reporting instead that alco-

holics see themselves as more depressed, tense, etc. while drinking. While important methodological failings, chief among which was reliance upon self-reported measures, weaken the overall validity of these findings, we nonetheless hypothesized that tension level, reflected by muscle action potential level, would in this study correlate negatively with blood alcohol levels and, further, that there would not be a significant relationship between a subjective units of disturbance scale (Wolpe, 1969) and either blood alcohol level or tension level.

Effects of Electromyographic Feedback Training upon Muscle Tension Levels

Several investigators have reported significant decreases in muscle tension after using electromyographic feedback techniques (Budzynski and Stoyva, 1971; Wickramasekera, 1972). These techniques have also been used to increase the precision of measurement of muscle tension in systematic desensitization studies. Questionable success has resulted from the use of systematic desensitization (a procedure which relies upon relaxation training) with chronic alcoholics (Hedgeberg and Campbell, 1972; Kraft and Al-Issa, 1967, 1968; Storm and Cuttler, 1968), perhaps because of failure actually to decrease tension levels in experimental subjects. It was hypothesized that electromyographic feedback training, when compared with an attention placebo condition, would produce a statistically significant decrease in muscle tension level.

Effects of Electromyographic Feedback Training upon Drinking Behavior

If alcohol serves a tension-reducing function, then training in an alternate means of coping with tension should produce a decrease in alcohol consumption by chronic alcoholics. As a result, it was hypothesized that electromyographically-induced muscle relaxation could serve as an alternate to drinking as a coping response to stress and predicted that Ss taught relaxation skills would be less likely to consume alcohol because they no longer need it to achieve tension reduction.

DESIGN AND PROCEDURE

Subjects were all chronic alcoholic men who met selection criteria which ensured that they were in good physical and psychological health. No subject professed a desire for treatment for his alcoholism.

The entire study, which lasted 41 days, took place at the Alcohol Behavior Research Laboratory (ABRL). It was divided into ten separate phases, as shown in Table III.

1. Orientation (3 days)

Ss were oriented to the procedures and "house rules" of the ABRL and received a complete physical examination. In addition, a sample of each S's *frontalis* muscle action potential (EMG) was taken three times each orientation day — in the morning, afternoon, and evening — according to a standard procedure recommended by Budzynski and Stoyva (1969).

TABLE III
OUTLINE OF STUDY II

Phase	Condition	Duration
1	Orientation	3 days
2	Baseline drinking	12 days
3	Detoxification	2 days
4	Training A	6 days
5	Free drinking A	4 days
6	Detoxification	1 day
7	Training B	6 days
8	Free drinking B	4 days
9	Detoxification	1 day
10	Debriefing	2 days
Total		41 days

Measurement of muscle action potential levels was accomplished by the Bio-Electric Information Feedback System (BIFS; Model B-1, Bio-Feedback Systems, Inc., Boulder, Colorado). This instrument was also used to provide Ss with feedback on level of muscular relaxation during the training phases.

2. Baseline Drinking (12 days)

In order to have a relatively stable estimate of pre-study *ad lib* drinking behavior, Ss were permitted free access to beverage alcohol (86 proof Bourbon Whiskey) for a 1-day period. Drinks were poured automatically by dispensers in each S's room and at the bar. A computer provided E an hourly print-out of the time and place (bar or room) of each drink dispensed. Alcohol consumption was restricted to an upper BAL limit of 250 mg/100 cc to avoid the deleterious physical effects of inordinately high concentrations of alcohol in the blood.

EMG basal measurements continued as before during this period.

3. Detoxification (2 days)

During this period Ss were not given free access to alcohol. To assist in detoxification, and to avoid serious withdrawal sequelae, Ss were first permitted single shots of alcohol every three hours. They were then "tapered off" this schedule until their BALs were zero by the evening of the last detoxification day.

4. *Training A (6 days)*

Before the experiment began, the four Ss had been randomly assigned to one of two treatment sequences. Two different treatment conditions, an EMG feedback condition and an attention placebo condition, were employed in this regard. Table IV summarizes the assigned treatment sequence for each S during Phase 4 (Training A) and Phase 7 (Training B); this design comprised a replicated 2x2 Latin Square.

TABLE IV
SUBJECT ASSIGNMENT TO TREATMENT CONDITIONS

	Subjects			
	1	2	3	4
Training	EMG	Attention	EMG	Attention
Period A	Feedback	Placebo	Feedback	Placebo
Training	Attention	EMG	Attention	EMG
Period B	Placebo	Feedback	Placebo	Feedback

Each training period (Phases A & B) lasted six days and contained a sequence of 14 training sessions. The first four of these sessions were held the first training day; the other ten took place the remaining five days at a rate of two per day. The sequence of EMG feedback training sessions adhered to the following plan:

a) *Taped Relaxation-Group (one 15-min. session).* The two Ss in this sequence attended a relaxation training session in the dayroom during which they listened to a 14-min. cassette recording of relaxation instructions which emphasized internal proprioceptive cues to deep muscle relaxation (e.g., warmth, heaviness). A staff member concurrently modeled the appropriate exercise for each muscle group.

b) *Taped Relaxation-Individual (one 15-min. session).* Each S was then given a cassette player, told to practise relaxing in his room by following the directions on the tape, and informed that he would be monitored via closed circuit television to insure his compliance with the relaxation instructions.

c) *EMG Relaxation (one 20-min. session).* S was brought into the experimental room and instructed to sit in a large comfortable reclining chair. On being attached to the BIFS Unit, he was then asked by a staff member to progress systematically through the relaxation procedure he had learned. Once S had completed this relaxation sequence he was instructed to remain relaxed for a short period of time. In fact, this period encompassed ten complete 64-sec. EMG trials. This 20-min. session served both as further relaxation practice and as an introduction to the feedback apparatus.

d) *Forearm Feedback (three 60-min. sessions).* For the next three sessions S was provided feedback on the level of muscle relaxation in his right *extensor* forearm muscle.

After application of adhesive electrodes to *S*'s right extensor forearm (Lippold, 1967), *S* was instructed to relax his forearm as best he could, while he was provided feedback on his level of muscular relaxation. Auditory feedback, delivered through a set of standard headphones, consisted of a tone whose pitch varied directly with degree of muscle tension. Visual feedback was a light display; a green light corresponded to low tension level, a yellow light to moderate tension, and a red light to high tension. *S* was told that his task was to keep the tone low and the light green. Then as each *S* progressed through the three training sessions the sensitivity of the BIFS was modified during the 20-second rest period so that he maintained the green light and low tone for approximately 80 per cent of the trial. This was done to enable *Ss* to reach deeper and deeper levels of muscular relaxation as they "worked" harder and harder to maximize the low tone and green light.

Each 60-minute training session contained three sets of ten 64-second trials. A four minute break between each set was also programmed. Feedback relaxation was introduced via forearm muscle training for two reasons: this muscle has proven relatively easy to relax in previous demonstrations (Budzynski and Stoyva, 1971) and hence provides successful experience with the procedure; it also alerts *Ss* to internal cues to relaxation which can then be transferred to the learning of frontalis relaxation.

e) *Frontalis Feedback (eight 60-min. sessions)*. At the seventh training session headband electrodes were placed over *S*'s frontalis muscle. With the same feedback conditions in operation, *S* was instructed to relax his forehead and face as completely as possible in order to keep the tone low and the light green. As before, each session included three sets of ten trials.

The *frontalis* muscle was chosen for feedback training since it has been demonstrated that frontalis relaxation mediates relaxation in the upper half of the body (Budzynski, Stoyva and Adler, 1970) and, further, can serve as a reliable index of general relaxation throughout the entire body.

The sequence of placebo (attention control) training sessions adhered to the following equivalent plan:

a) *Placebo Tape-Group (one 15-min. session)*. *Ss* were instructed to attend a taped presentation similar to that given the two feedback training *Ss*. All feedback and placebo conditions were the same except that the placebo tape to which *Ss* listened contained excerpts from *The Abnormal Personality* (White, 1948). Selections were taken from the section on alcoholism; this tape lasted 15 minutes. *Ss* were told to reflect on the content of the taped presentation and to apply its insights to their own life.

b) *Placebo Tape-Individual (one 15-min. session)*. *Ss* were requested to play the tape alone that they had heard together, and to use that time again to think about the content of the tape.

c) *Placebo Session (one 20-min. session)*. *S* was brought into the experimental room and told that his "integrated bio-potential level" would be monitored via the headband electrodes while he thought about the tape he had heard earlier. During this time *E* was actually monitoring *S*'s integrated muscle action potential level via the BIFS unit.

d) *Forearm Placebo (three 60-min. sessions)*. Adhesive electrodes were attached to *S*'s right forearm extensor muscle at the start of each session. As with feedback training *Ss*, placebo *Ss* were given the headphones and shown the light display. However, they were instructed to use this time to reflect on the tape and their drinking life rather than to try to maintain a low muscle tension level. They were further told that the headphones would help block out extraneous noise and that the light display would help them

contemplate. In fact, the headset was turned off and the light display was driven by a computer program which randomized the percent of red, green, and yellow lights displayed.

e) *Frontalis Placebo (eight 60-min. sessions)*. *S* was given the same instructions concerning his task and the role of the headset and light display. The same conditions of disengaged headset and random light display were in effect. The sessions, as before, lasted for three sets of ten trials each; again, as before, *E* recorded tension levels for each trial during each session.

5. *Free Drinking A (4 days)*

With the completion of Training A, *Ss* were again permitted *ad lib* access to beverage alcohol. Free drinking began for all *Ss* at 0700 the morning after the last training session during Phase 4. As in the Baseline drinking phase *Ss* were permitted free access to alcohol up to a BAL of 250 mg/100 cc. EMG basal measures followed the same schedule as that imposed during the Baseline drinking Phase.

6. *Detoxification (1 day)*

The same detoxification procedure as that employed after the Baseline drinking Phase was then imposed.

7. *Training B (6 days)*

The conditions and measurements during this phase were exactly the same as those during Training A, except that *Ss* 1 and 3 were placed in the placebo condition while *Ss* 2 and 4 received EMG feedback training.

8. *Free Drinking B (4 days)*

The conditions and measurements during this phase were the same as those during Free drinking A.

9. *Detoxification (1 day)*

The conditions of this phase were the same as those during Phase 6.

10. *Debriefing (2 days)*

RESULTS

Relationships Among Muscle Tension (EMG), Blood Alcohol Level (BAL), and Subjective Disturbance (SUDS)

Thirteen of 40 potential correlations of EMG and BAL reached significance. This number

of significant relationships between EMG and BAL exceeds the number that would be expected by chance alone (2 of 40, at the 5% level). Eleven of these 13 significant correlations were negative. Finally, 29 of the 40 BAL-EMG correlations were negative. We conclude, as a result, that the predominant relationship between BAL and EMG revealed in this study was of increasing BAL and decreasing EMG.

Ten of 40 pairings of BAL and SUDS reached significance; of these, 8 of the 10 were positive. This number too exceeds chance levels. In addition, 26 of the 40 BAL-SUDS correlations were positive. We believe, as a consequence, that it can fairly be said that this study revealed a consistent relationship between BAL and SUDS characterized by increasing BAL and increasing SUDS.

Effects of Electromyographic Feedback Training on Frontalis Tension Levels

A Model II 2x2 replicated Latin Square ANOVA for repeated measures performed upon integrated muscle tension level data for all Ss during Training Phases A and B revealed that Ss reached significantly lower tension levels during feedback training than during the attention placebo condition ($F = 867.89$, $df = 1/2$, $p < .01$).

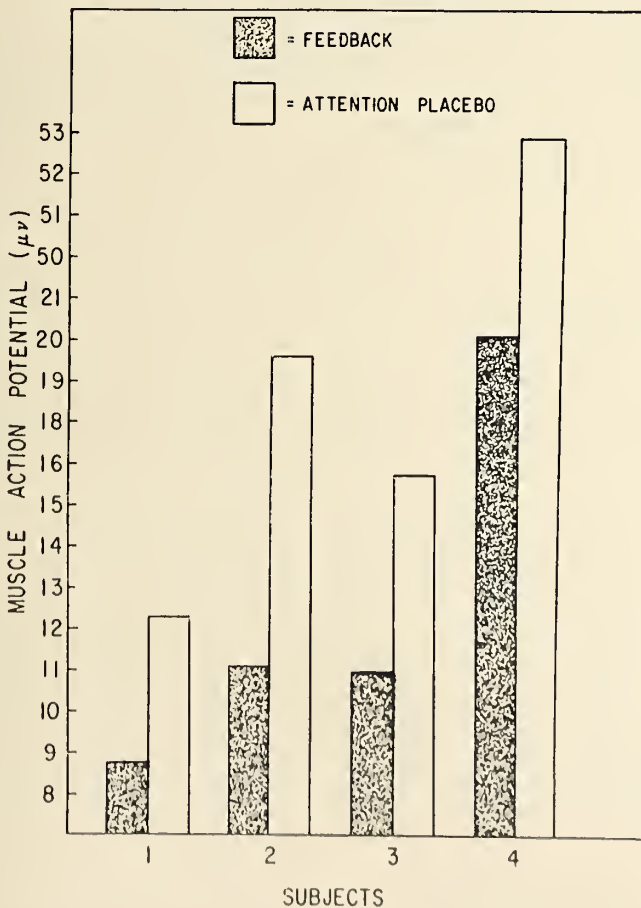


Figure 4. Average muscle action potential levels following feedback and attention placebo conditions during Study II.

Figure 4 compares the average muscle action potential levels achieved by each of the four Ss during the feedback and attention placebo conditions. Tension level was considerably lower for all four Ss during feedback training than during the attention placebo condition. Ss 1 and 3, who received feedback training before placebo training, showed slight evidence of a "carry-over" of training from the feedback to the placebo condition in that both Ss' tension levels during placebo training were lower than Ss' 2 and 4 placebo tension levels.

Effects of Feedback Training upon Drinking Behavior and Self-Report Measures

Two x two Latin square ANOVA's for repeated measures were performed on the data gathered during the post-training Free drinking periods (5 and 8). They revealed the following:

1) *Blood alcohol level.* Subjects reached significantly lower blood alcohol levels following feedback training than following the placebo condition ($F = 29.96$, $df = 1/2$, $p < .05$). Blood alcohol levels increased over the four days of the drinking periods ($F = 6.268$, $df = 3/6$, $p < .005$). No other effects or interactions reached significance.

2) *Computer drink data.* An ANOVA performed on the number of drinks ordered did not reveal any significant training effects. In other words, Ss ordered as many drinks following EMG feedback training as following placebo training.

3) *Tension Level.* All Ss' muscle action potential levels were monitored during all drinking days. Analysis of these data was based on mean peak-to-peak electromyographic responses for five 64-second trials. This analysis revealed significant subject differences in mean tension level ($F = 30.84$, $df = 3/2$, $p < .01$).

DISCUSSION

Relationships between BAL and EMG

Our data support the widely-held view that muscle tension is negatively correlated with blood alcohol level. The relationship between increasing BAL and decreasing tension level revealed in this study is thus consistent with the tension-reduction model of alcoholism etiology which, simply stated, assumes that alcohol reduces tension.

Previous investigation of the TRH with infra-human organisms employed diverse measures of tension and tension-reduction (Cappell and Herman, 1972); for both reasons, the results of these studies provide only equivocal support for the TRH. The results of this study, however, may contribute to a more definitive answer to the question of the validity of the TRH. To this end, every such study reviewed by Cappell and Herman (1972) that failed to support the TRH employed acute alcohol administration. Our findings, indicating that decreasing muscle tension does not occur every day during a drinking period, suggest that studies of the TRH that employ acute alcohol administration may not be fully exploring the tension-reducing quality of alcohol.

Relationships between BAL and SUDS.

The predominant positive correlation between BAL and SUDS identified in this study is

consistent with findings from previous studies of alcoholics' self-reported mood while drinking (Davis, 1971; Nathan and O'Brien, 1971; Tamerin and Mendelson, 1969) to the effect that as alcoholics become more intoxicated, they report higher levels of anxiety, depression, and other untoward affective behaviors. These investigations have been interpreted to contradict the TRH in that, if alcohol reduces tension, then Ss should report decreased, not increased, affective disturbance. Our findings concerning correlations between BAL and EMG and those between BAL and SUDS, however, suggest that relationships among intoxication, tension, and subjective disturbance are more complex than previously believed.

Effects of Electromyographic Feedback Training

The results of the Latin square ANOVA supported the hypothesis that electromyographic feedback training is superior to an attention placebo condition in producing a decrease in muscle tension level. Ss serving as their own controls attained lower muscle tension levels with EMG feedback than in the attention-placebo condition. Ss also reached lower tension levels during EMG feedback than during the placebo, the more sessions, series and trials they received. In other words, EMG feedback Ss showed a lowering of tension level the more training they received, whereas placebo Ss did not show a comparable decrease in tension level even with practice. The potential utility of EMG feedback training for patients undergoing systematic desensitization is but one possible extension of these results to the clinical scene.

Effects of Training upon Drinking Behavior and Self-Report Measures

Our results provide equivocal support for the hypothesis that EMG feedback training can serve as an alternate response to drinking. Thus, while the ANOVA revealed that Ss had significantly lower BALs after feedback training than after placebo training, the computer drink data showed that Ss did not differ in the number of drinks they ordered following the two conditions. In other words, Ss seemed to be drinking as much but enjoying it less!

Several factors may have contributed to the significant decrease in BAL we saw during feedback training in the absence of a concomitant decrease in number of drinks ordered by Ss. First, the computer records only drinks *ordered* by Ss, not drinks actually *consumed*. Ss may have ordered drinks they did not consume during the post-feedback drinking period. Second, Ss may have consumed more food during the post-feedback drinking period, depressing the rate at which alcohol entered their blood streams and thus producing lower BALs over time. Third, Ss may have altered their usual patterns of alcohol consumption after EMG feedback training. Recent research indicates that alcoholics differ from social drinkers on several parameters related to drinking which relate to speed of intoxication (Sobell, Schaefer and Mills, 1972; Schaefer, Sobell and Mills, 1971). These include amount of time to finish drink, amount of alcohol consumed per sip, and style of drink (mixed versus straight).

The latter explanation of our paradoxical data would "make sense" if tension reduction played an important role in the maintenance of alcohol consumption by alcoholics. If Ss experienced less tension following feedback training, then they would be less likely

to exhibit behaviors leading to rapid intoxication (hence rapid tension reduction). In other words, training in and maintenance of relaxation may serve as an alternate response to drinking.

STUDY III: BLOOD ALCOHOL LEVEL ESTIMATION AND CONTROLLED DRINKING

Lovibond and Caddy (1970) recently reported having trained outpatient alcoholics first to estimate blood alcohol levels from proprioceptive cues and then to modulate consequent *ad lib* drinking. An extensive follow-up of the large group of alcoholics trained within this paradigm encouraged the authors to believe that discriminated blood alcohol level training represents an extremely promising approach to behavioral treatment to induce abstinence. The study has, however, recently been questioned on design and methodology grounds (Nathan, 1974). Of particular relevance to the study to be reported here is the fact that the Lovibond and Caddy study relied on self-reports from Ss for follow-up purposes, a design factor that raises a serious question about the reliability of the encouraging follow-up data that were reported. Another design problem in their study was that Ss were provided with three BAL curves (to familiarize them with anticipated BAL fluctuations) before BAL discrimination training began. It seems entirely possible, however, that at least some of the Ss who then appeared able accurately to estimate BAL did so with these curves in mind, rather than as a function of the visceral cues to which they had also been alerted.

The study to be reported here was designed to explore more fully than before the extent and determinants of alcoholics' presumed ability to modulate their own drinking behavior on the basis of blood alcohol level estimation. To this end, baseline drinking behavior, the effects of discrimination training, and subsequent success in maintaining control over drinking with and without associated feedback and reinforcement contingencies were all directly observed in the Alcohol Behavior Research Laboratory. Phase I of the study, an extended replication of Lovibond and Caddy's BAL estimation procedure, aimed to train Ss accurately to estimate BAL between 0 and 150 mg/100cc. Phase II then focused on training Ss to reach and maintain a "target" BAL (70-90 mg/100cc.) that would, if maintained outside the laboratory, permit them to re-enter productive society.

DESIGN AND PROCEDURE

Four male volunteers were chosen from among alcoholic inpatients in New Jersey public hospitals. All Ss met selection criteria which ensured their status as chronic alcoholics, their good physical and psychological health, and their strong interest in learning to control their drinking.

Ss were brought directly to the Alcohol Behavior Research Laboratory (ABRL), Rutgers University, for the 36-day study which followed.

Phase I: Estimation Training

The overall design of the study is summarized in Table V. The goal of Phase I of the

TABLE V
DESIGN OF STUDY III
PHASE I ESTIMATION TRAINING

B1		T1	T2	T3	B2
Estimation Baseline		Training Cycles			Estimation Baseline
No Fdback No Reinf.	Continuous Feedback	Variable Feedback	Var. Fdback	No Fdback No Reinf.	No Fdback No Reinf.
	No Reinf.	No Reinf.	Contingent Var. Reinf.		
Days 1-2		Days 3-4	Days 5-6	Days 7-8	Days 9-10

PHASE II: CONTROL TRAINING					
BC1	RS	C1	C2	C3	BC2 G
Control Baseline	Reinf. Sampling	Narrowing to Accept. Range (70-90mg/%)	Baseline with Contingency	Contingency Fade Out	Control Baseline Target Generalization
Ad Lib Drinking	Programmed Drinking	Partially Programmed Drinking	Ad lib Drinking		
No Fdback No Reinf.	Variable Feedback Variable Reinforcement Target: 80mg/100cc			Fade Out	No Feedback No Reinforcement Var. Target
Days 11-13	Days 14-15	Days 16-22	Days 23-25	Days 26-28	Days 29-34 Days 35-36

study, which lasted 10 days, was to train Ss to estimate BAL accurately. Target behavior in this context was defined as 75 per cent of all of a S's BAL estimates falling within 20mg/100cc. of his actual BAL. Throughout Phase I, drinking was programmed in two-day cycles to cause Ss' BALs to rise slowly to 150mg/100cc. during the first day, to remain at approximately that level overnight, and then to fall through the next day to a zero BAL.

During the first two baseline days of Phase I (B2), Ss estimated BAL without being provided feedback of actual BAL. In every case their estimates (at least 10 per day per S) were made prior to actual BAL measurement, both when a drink (86-proof blended whiskey) was dispensed as well as at other scheduled times throughout the day. Ss received minimal information on which to base BAL estimates during the baseline period. Told to convert their estimated level of intoxication into a number between 0 and 40, they were given the additional instruction that 0 was to represent "cold sober" and 40 "extremely drunk, probably drunker than any of you has ever been."

The next three two-day cycles (T1, T2, T3) were devoted to training in BAL estimation. During these six days Ss were continually alerted to the emotional and physical correlates of specific BAL levels: each time a S received BAL feedback, he discussed the cues he had used to make his judgment with a staff person. Staff members also reinforced all accurate and/or improving BAL estimations verbally.

The first training period (T1) differed from the baseline period in that feedback of Ss' actual BALs was provided after each of their own BAL estimates. During the second training cycle (T2), feedback was given intermittently, on a random schedule averaging 50 per cent of trials. This change permitted direct comparison of accuracy on trials following feedback versus those unaccompanied by feedback. The third cycle (T3) of Phase I marked the first time reinforcement (delivered as points convertible into subsequent alcohol or money) was made contingent upon accurate BAL estimation; points previously had been awarded noncontingently. Intermittent feedback on BAL continued to be given during T3, although now yoked with the point contingency.

The final two days of the estimation phase (B2) replicated the first baseline cycle (B1); point reinforcement for accuracy, feedback on BAL, and attention to physical and emotional correlates of BAL were all withdrawn at the beginning of B2 in order to reestablish the experimental conditions which applied during B1.

Phase II: Control Training

The goal of Phase II (which lasted 26 days) was to train Ss to use their BAL estimates as discriminative stimuli for decisions about when and how much to drink — as primary means for controlling their own drinking behavior. Control was ultimately defined as the ability to maintain a BAL at the target of 80mg/100cc.

During the first two days of the first Phase II baseline period (BC1), Ss drank from 8a.m. until 2p.m. in the attempt to attain the target BAL of 80mg/100cc. Ss were then instructed to remain as close as possible to the desired 80mg/100cc. from 2p.m. until midnight. No feedback on BAL was given during these times. Drinks were dispensed on request during this time; only if a S reached an (undisclosed) upper limit of 150mg/100cc. was he refused a requested drink. On the third day (BC1a) of this period, Ss were actually brought to the target BAL of 80mg/100cc. at 2 p.m., after which they were to maintain this target level through the rest of the day.

The baseline period was followed by a two-day "reinforcement sampling" period (RS) in which drinking was programmed in such a way that each *S* experienced all contingencies associated with the two distinct sub-routines which were also introduced at that time. (1) At a *Drink Call* *S* estimated his BAL, provided a breathalyzer sample, drank his allotment of beverage alcohol (either one, two, or three ounces of beverage alcohol), and then was told how much the drink had "cost." Drinks were free for a *S* whose BAL was below 80mg/100cc; above 80mg/100cc. they became progressively more costly. In other words, a drink's cost represented partial feedback on BAL. (2) During a BAL Check, drinks were not dispensed but points were earned or lost depending on the discrepancy of a *S*'s actual BAL from target; exact BAL feedback was given at these times.

The core of the control training procedure (periods C1, C2, and C3) employed three converging behavioral control procedures: 1) the locus of control over drinking gradually shifted from completely external (that is, totally programmed by E) to completely subject-controlled; 2) the range of positively reinforced BALs was successively narrowed closer and closer to the ultimate BAL target of 80mg/100cc; 3) all reinforcement and feedback were gradually faded out.

To this end, while *Ss* had no control over timing or amount of drinking during the RS period — E completely determined drinking times and amounts — *Ss* regained partial control over these matters during C1. While drinks were available only at predetermined times during C1 (during Drink Calls), *S* could choose to have 0, 1, or 2 drinks at these times. Complete control of drinking was then given *Ss* during C2 and C3.

Concurrent with this gradual change from complete to partial to no external control of drinking was the institution of a "narrowing of range" shaping procedure for targeting of BAL. At the beginning of C1, *Ss* were positively reinforced with points for BALs that fell within a very wide BAL range (30 to 130mg/100cc). BALs falling outside this acceptable range caused a loss of points, with more points lost for greater deviations from the range. By prearranged formula, a new reinforcement range was calculated each day, dependent on a *S*'s previous day's performance, narrowing to a final positively-reinforced range of 70 to 90mg/100cc. by the end of C1. During C2, *Ss* were to maintain this "target" range, albeit under contingency (point) control. At the start of C3, the cues to controlled drinking provided by BAL feedback and point reinforcement began gradually to be withdrawn; by the end of this three-day period, these cues were completely absent. The prevailing experimental conditions during BC2 replicated exactly those in BC1, the pretraining Phase II baseline.

During a final two-day test period (G), *Ss* were asked to maintain themselves at different target levels. The addition of this stage to the study was prompted in part by two *Ss*' observations that the 80mg/100cc. target level was inappropriate for them: one wished it to be lower, the other, higher. On the first day of this period, as a result, *Ss* were assigned to the BAL target level they had requested (40, 80, or 120mg/100cc); on the second day, they were asked to attempt to maintain a different level.

Follow-up

To assess drinking behavior after the project ended, each *S* was given 40 postcards to be returned at the rate of one each day. The cards were designed to provide specific information about self-control of drinking and amount of alcohol consumed. Data to corroborate the postcard information was sought from each *S*'s closest family member or friend. At 10 weeks post-study, personal interviews were arranged with each *S* for the same purpose.

RESULTS

Estimation Training

Phase I. Figure 5 shows that during the Phase I baseline period (B1), Ss were unable to estimate BAL accurately. However, when BAL feedback was subsequently introduced on the first day of T1, three of the four Ss (Ss 1, 2, and 3) immediately increased the accuracy of their BAL estimates to a discrepancy level averaging 14mg/100cc. No additional gain in estimation accuracy for any of these three Ss occurred after this first day of estimation training. By contrast, S4's estimation accuracy continued to improve to the end of T2, though it never attained the levels of estimation proficiency reached by the other three Ss.

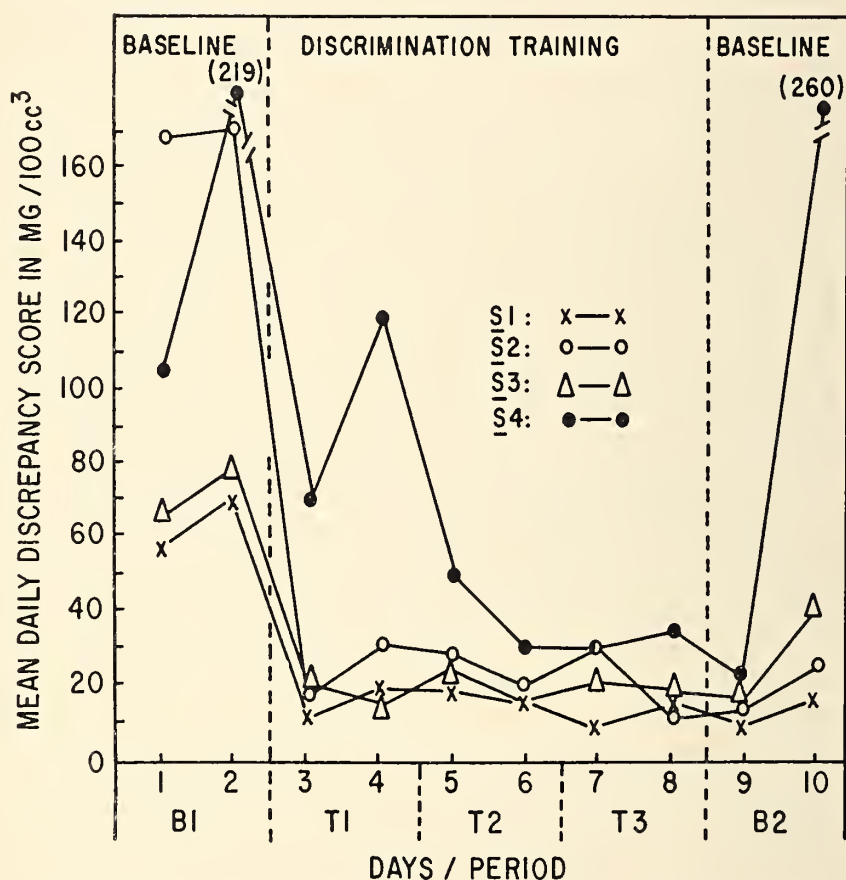


Figure 5. Mean daily discrepancy scores for Study III subjects during discrimination training.

On the first day baseline conditions were reinstated after completion of Phase I estimation training (on the first day of B2), Ss maintained approximately the same high level of estimation accuracy that each had attained during training. On the following day, however, all Ss' accuracy deteriorated. Though Ss 1, 2, and 3 remained largely accurate, with discrepancies averaging only 30mg/100cc., S4's estimates became essentially random, averaging 257mg/100cc. from actual BAL.

Phase II. Accuracy of BAL estimation was also assessed through Phase II. Figure 6 shows these data, plotted by periods rather than by days. The last two periods of Phase I (T3, B2) are included in Figure 6 for comparative purposes.

Figure 6 shows that during BC1, when Ss² changed from programmed to *ad lib* drinking, their BAL estimation accuracy abruptly deteriorated. On the third day of Phase II (BC1a), drinking was programmed so that Ss were brought to 80mg/100cc. by 2p.m. Ss then began *ad lib* drinking, trying to maintain that BAL for the rest of the day. As a consequence, two Ss improved their estimation accuracies and the third returned to previous accurate levels during BC1a.

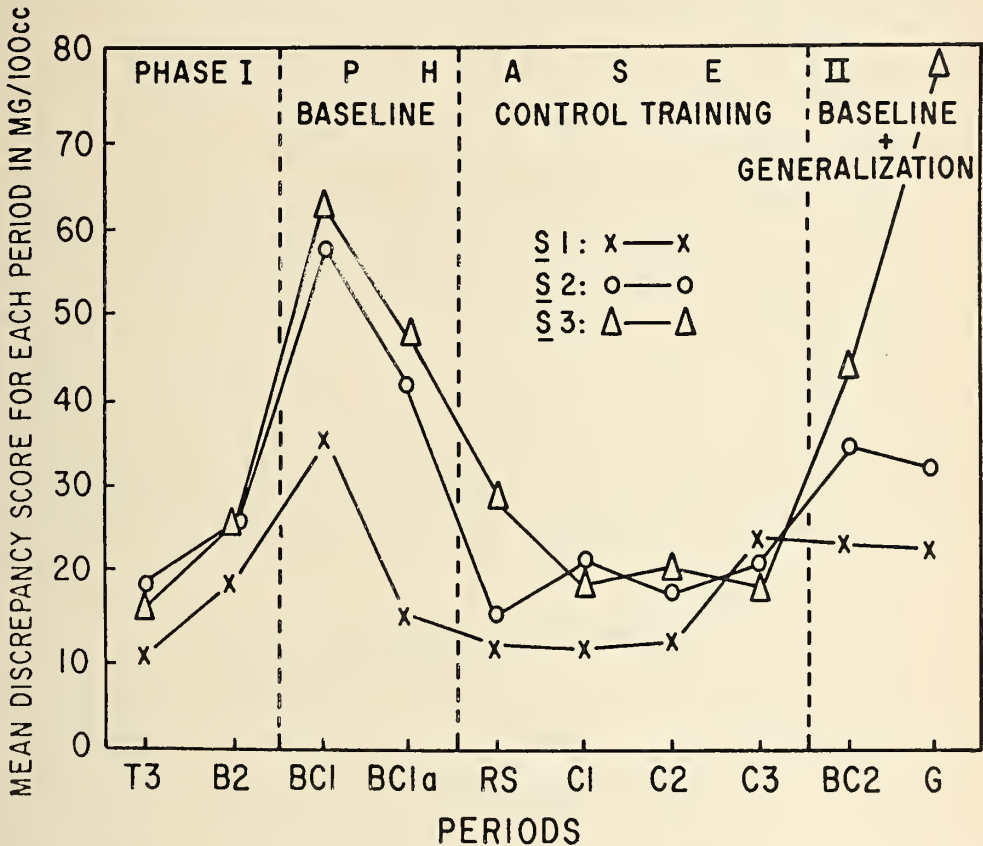


Figure 6. Mean daily discrepancy scores for Study III subjects during control training.

During the ensuing reinforcer sampling period (RS), when BAL feedback, point reinforcement, and programming of beverage alcohol were reinstated, and throughout the subsequent three training periods (C1, C2, C3) — so long as even a residual of BAL feedback remained — Ss accurately estimated BAL. Only during the last two periods of Phase II (BC2 and G), from which feedback and reinforcement were completely withdrawn, did estimation accuracy again decrease markedly.

²S 4, whose performance through the study had deviated from that of the other three Ss, had also been showing psychotic-like behavior from the first drinking day. By the 10th day of the study, his behavior had become so disruptive that the decision to discontinue him from the study had to be made.

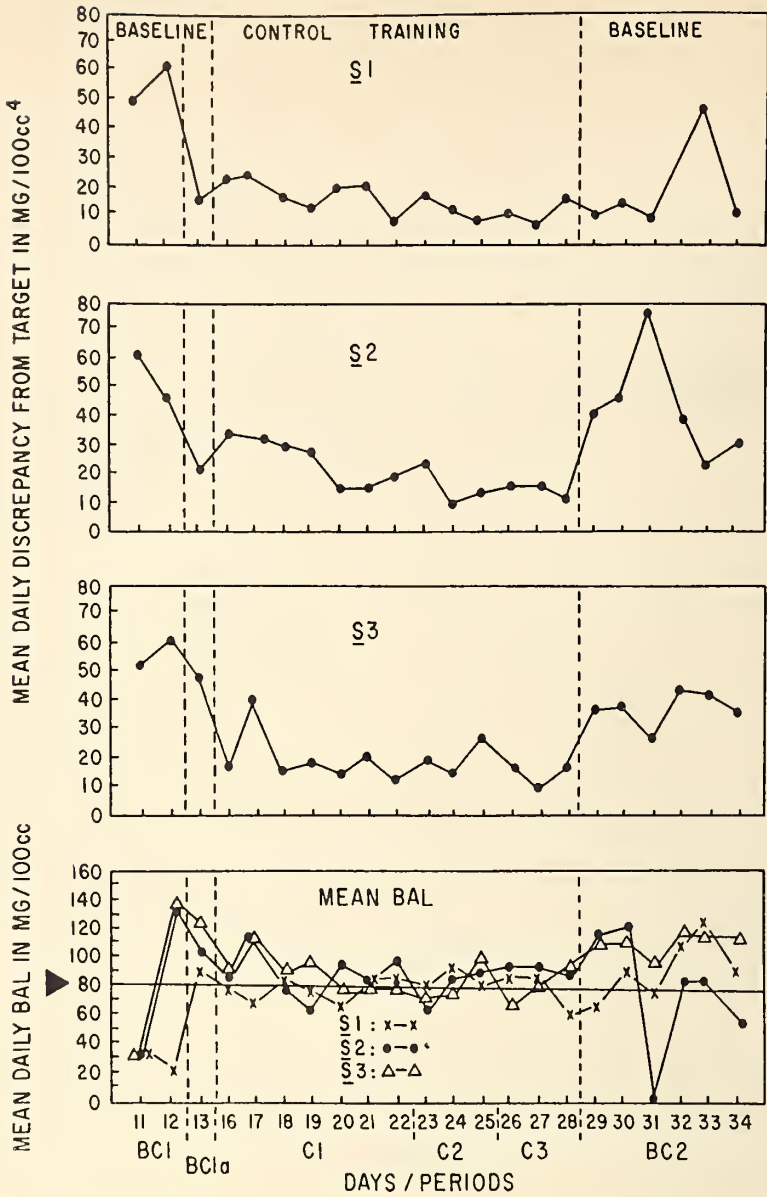


Figure 7. Mean daily discrepancy from “target” blood alcohol levels during control training in Study III.

Control Training

Figure 7 shows that Ss did not successfully “target in on” the 80mg/100cc. criterion during the first two days of Phase II baseline (BC1), when reinforcement for doing so was not provided. To determine whether this “off-target” behavior stemmed from problems in reaching or in maintaining target BAL, drinking on the first half of the third day was programmed so that all Ss started *ad lib* drinking again the second half of that day at the target BAL: 80mg/100cc. Two out three Ss then altered their drinking behavior to come closer to the target BAL.

During the first segment of control training (C1), reinforcement contingencies were

successively narrowed to bring Ss' drinking closer and closer to the ultimate BAL target of 70-90 mg/per cent. Figure 7 shows that Ss' drinking responded to these changing demands. By the last three days of this period (days 20-22), all Ss were demonstrating controlled drinking in that all mean daily discrepancy scores were within 20mg/100cc. of the target level of 80mg/100cc.

During the remaining periods of the study (C2, C3, BC2, and G), Ss assumed increasing responsibility for scheduling times and amount of alcohol intake. During C2 and C3, BAL feedback and reinforcement were still provided all Ss; during that time, drinking behavior remained close to the target BAL. As Figure 7 shows, however, this high degree of control disappeared when reinforcement contingencies and feedback were removed during BC2.

Follow-up

Of the three Ss who completed the study, two (Ss 2 and 3) returned daily post cards for 40 days after discharge. The same two Ss were also interviewed after 80 days. Corroborative data from members of their families were also obtained. S1, who returned only one postcard, was also unavailable for the follow-up interview. It was known, though, that he had resided at the local Salvation Army shelter for all but three of the 80 post-study days, permitting an adequate follow-up of his drinking to take place.

Summary follow-up data revealed that one S had been able to maintain a controlled pattern of drinking through the follow-up period, another had remained abstinent during much of the period by virtue of his residence at a Salvation Army Shelter, and the third had spent much of his post-treatment time drinking heavily, without apparent control.

DISCUSSION

While this study provided additional evidence to support prior findings that alcoholics can, under certain circumstances, learn to control their drinking, it also reaffirmed Lovibond and Caddy's findings that alcoholics can learn to make accurate estimations of blood alcohol level, though contrary to their report that this process takes only two hours, we found that it required a good deal longer than that. We also found that feedback on blood alcohol level, whether intermittent or continuous, accompanied by explicit reinforcement or not, appeared to be the controlling stimulus for accurate BAL estimation by our Ss, contrary to Lovibond and Caddy's belief that their Ss had depended upon visceral cues for this purpose. Finally, the new study questioned the determinants of Lovibond and Caddy's positive data (21 of 28 alcoholics drinking socially on follow-up), positing this outcome to have depended as much on undefined expectancy or demand variables as on BAL discrimination training. The basis for questioning the prior findings was that the ability of Lovibond and Caddy's Ss accurately to estimate BAL was not tested again after it was first established during the two-hour discrimination training period.

SUMMARY AND CONCLUSIONS

The projects described here were designed for two purposes. One was to extend and

recast results of prior related studies. The other was to add to a growing literature concerning efforts to train chronic alcoholics to drink in a controlled fashion. The results of these studies are sufficiently positive to encourage further exploration of the parameters of controlled drinking by alcoholics; they also highlight a need for explicit efforts to apply these or other comparable methods outside the laboratory setting, in the all-important effort to enable generalization of laboratory-induced changes in drinking behavior to the natural environment. We are convinced, in other words, that enough data have been gathered to justify the optimistic view that controlled drinking may be a realistic goal for some alcoholics, perhaps those for whom efforts to reach and maintain abstinence have repeatedly failed.

From a strictly technical point of view, these studies also confirm the value of a clinical research design that permits return to baseline conditions after a "treatment" intervention. This design, technically of the ABA or ABABA variety, allowed us to say with some certainty that cessation of aversive escape conditioning in Study I (that is, a return to the baseline condition) was not followed by a change in drinking behavior as compared to preconditioning drinking levels, that withdrawal of contingent shock, again during Study I, was associated with a resumption of previous high levels of drinking; that withdrawal of feedback on blood alcohol level during Study III was correlated with a reduction in the accuracy of blood alcohol level discrimination; and that a "return to baseline" during Study II revealed that electromyographic feedback more effectively reduced prestudy tension levels than the attention placebo condition.

While our provision for reversal of experimental conditions and return to baseline conditions hardly represents a new design discovery, this provision has not bulked large in the experimental treatment literature on alcoholism. That is, few investigators who have used aversive escape conditioning to try to alter subsequent drinking behavior by alcoholics or have endeavored to train alcoholics to drink in a controlled fashion have also directly measured the effects of their interventions before releasing their patients to the environments from which they came. As a result, it has not been possible to conclude with assurance that the positive outcome data some of these researchers have reported were a proven function of their interventions, since a whole host of environmental variables operative post-intervention may have influenced subsequent drinking outside the laboratory.

Although a "return to baseline" in the laboratory permits only an approximation of subsequent drinking behavior outside the laboratory, we believe that one must be able to demonstrate the effectiveness of an intervention within the laboratory, (where cues to positive change in drinking behavior are strongest), before asserting that posttreatment changes in drinking behavior are in fact direct functions of that intervention.

ACKNOWLEDGEMENT

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Suppression of Drinking and Facilitation of Prosocial Behavior in Residential Treatment Programs for Alcoholics

Miriam Cohen¹

All forms of treatment for alcoholics have as their aim the reduction of drinking, but the procedures used to pursue this goal vary considerably. In most residential treatment programs it is assumed that alcoholics' drinking results from intrapsychic conflict and that treatment should attempt to resolve this conflict. The two procedures used to reduce the probability of drinking during residential treatment are the absence of alcohol and talk with peers and staff members about one's psychological problems. The effect of these procedures on drinking during treatment is never evaluated.

In the past five years, two residential research programs for alcoholics have focused on identifying procedures which reduce the alcoholic's drinking while he is in a residential program. The assumption in this research has been that alcoholics' drinking may be governed in a large part by the events which follow it. The technique used to reduce drinking has been to make alcohol available and arrange the consequences of drinking so as to affect the probability of drinking. The effects of different consequences on the probability of drinking have been measured by counting the number of drinks the alcoholic consumes.

Residential research and treatment programs for alcoholics differ on four major dimensions: the availability of alcohol, the assessment of drinking, the consequences of drinking, and the behaviors focused on while the alcoholic is in residence.

In research programs, drinking has been permitted and assessed; the consequences of it have been programmed; and alcohol ingestion has been the behavior of primary concern. In treatment programs alcohol has not been readily available; drinking has only occasionally been assessed; and talk about drinking has been the major focus of therapy.

¹Boston Drug Treatment Program and Department of Psychiatry, Harvard Medical School, Boston City Hospital, Boston, Mass. 02118, U.S.A.

The purpose of this paper is to consider the rationale for incorporating some of the procedures used in residential research programs into residential treatment programs for alcoholics.

SUPPRESSION OF ALCOHOLICS' DRINKING: A. IN RESIDENTIAL TREATMENT PROGRAMS

Incidence of Drinking

Despite the fact that drinking during treatment has not been given widespread attention in the alcoholism literature, drinking by alcoholics during treatment must be very common. Alcoholics, by definition, drink too much, too often, and unless objective evidence to the contrary is provided, there is little reason to believe that drinking does not occur during residential treatment.

Of 17 articles in the alcoholism literature which describe residential treatment programs for alcoholics, 13 did not mention whether drinking occurred during the course of treatment. (Agrin, 1960; Androes and Whitehead, 1966; Belden, 1962; Corwin and Cunningham, 1944-45; Fox and Lowe, 1968; Jensen, 1962; Judge, 1971; Katz, 1964; Moore and Buchanan, 1966; Rossi, Stach and Bradley, 1963; Valles and Sikes, 1964; Voth, 1963; and Wilbur, 1966). The implication was that no drinking occurred during residential treatment. Four other articles indicated that drinking during residential treatment was a problem but they did not indicate the magnitude of it (Milton and Agrin, 1966; Ottenberg, 1969; Rothstein, Norton, Lahage, and Meuller, 1966; and Wenger, 1955).

The residential programs in which the incidence of drinking was investigated indicate that many alcoholics drink on more than one occasion during treatment. Moore and Ramseur (1960) describe a psychotherapy program for alcoholic inpatients, conducted on an open ward of a veterans' hospital in which many of the alcoholics drank consistently during treatment. The subjects were 100 male veterans, voluntarily admitted to the hospital because of a drinking problem. The average length of stay in the program was 105 days and the range of stay was from two days to 1½ years. Patients were selected who were thought to be good candidates for psychotherapy, and the cornerstone of the program was intensive individual psychotherapy. Patients were granted leave privileges at least twice a week. There were no scheduled consequences for drinking during the therapy program. Of the 100 alcoholics treated, 60 of them drank "consistently" (no definition of consistently was given) throughout the program and 15 were discharged from the program for bringing liquor into the hospital or drinking in the hospital.

Wolf, Foxwell, and Kurland (1965) investigated the incidence of unauthorized drinking on an alcohol rehabilitation unit, in a state hospital during a one year period. Any drinking on the ward was considered a violation of ward rules, which sometimes (the authors do not say how frequently) resulted in being moved to a closed ward. During a one year period, 423 alcoholic patients were admitted to the unit. Some of the patients were court committed and others were voluntary admissions. The average length of stay was 45 days. The therapy program consisted of AA meetings, group therapy, psychodrama, occupational therapy, a therapeutic community and self-government. Patients were permitted to leave the hospital grounds on evenings and weekends.

The investigators were interested in using unobtrusive measures to determine the incidence of unauthorized drinking, since they thought that any conspicuous measures of drinking would alter its frequency. Hence, they did not measure blood alcohol concentration levels. The three measures they used to estimate the incidence of drinking were

observations of a patient's status by ward staff, reports of the patient's drinking made by the unit chairman (a patient on the ward), and reports that the patient made of his own drinking to the research psychiatrist.

They found that 31 per cent of the 423 patients were known to have drunk on one or more occasions and an additional 4 per cent were suspected of drinking.

Five halfway house directors have also reported to me that drinking often occurs in halfway houses for alcoholics. However, the incidence of drinking is not known. Halfway house directors said official house policy is that residents are discharged for drinking, but they do not always apply this contingency.

Consequences of Drinking

When drinking occurred in the residential treatment programs just described, both the nature and magnitude of the consequences for it, as well as the schedule according to which the consequences were applied varied considerably within and between programs. Sometimes there were verbal reprimands for and discussion of drinking following its occurrence (Milton and Agrin, 1966). Sometimes the therapist emphasized the undesirability of drinking during the therapy session (Wenger, 1955, Moore and Ramseur, 1960). Sometimes drinking was penalized by withholding leave privileges, making the patient wear his pajamas, or requiring him to be accompanied to meals by another patient (Rothstein, Norton, Lahage and Mueller, 1966). Other procedures used in an effort to suppress drinking included ignoring the drinking, sending the drunk person to the sick room or a closed ward (Wolf, Foxwell, and Kurland, 1965), or discharging the offender from the program.

It seems that drinking often gains more staff attention for the alcoholic than sobriety or other productive behavior, in residential treatment programs. Probably the alcoholic's drinking in his or her natural environment had also mobilized attention from significant other persons. Such a contingency would favor an increase in drinking, by those persons who most hope to bring about a decrease in it.

SUPPRESSION OF ALCOHOLICS' DRINKING: B. IN RESIDENTIAL RESEARCH PROGRAMS

Two residential research programs for alcoholics, one at Baltimore City Hospital and one at Patton State Hospital, have focused on identifying procedures that reduce the alcoholic's drinking while he is in the hospital. Alcohol has been made readily available and the consequences of drinking have been programmed so as to affect the probability of drinking.

Events following drinking which have been used to suppress it, include loss of money, loss of social contact, loss of the opportunity to participate in an enriched environment, and the delivery of shock. The studies to be reviewed have been published separately in more detail elsewhere. However, they are recapitulated here because the collective results provide a convincing case that alcoholics' drinking can be suppressed by the appropriate programming of consequences, and these findings have implications for the design of residential treatment programs for alcoholics.

When money was the incentive for abstinence or controlled drinking, hospitalized alcoholics could turn down drinks (Cohen, Liebson, Faillace, and Speers, 1971). Four alcoholics had access to 24 ounces of 95 proof ethanol on several different days. The days on which they had the opportunity to drink were spaced two or three days apart. They

were offered money in amounts ranging from \$5.00 to \$20.00 if they would abstain completely for the day. If they drank on a particular day the amount they were offered on the next opportunity they had to drink was increased. Two alcoholics required \$7, \$12, and two others, \$20 to stop drinking for one day.

Using the same paradigm and the same subjects, two alcoholics were given priming doses ranging from six to ten ounces of alcohol on different days. If they were not paid to stop, they consumed all available alcohol. If they were paid to stop they stopped drinking, even after having drunk between six and ten ounces. As the priming dose of alcohol increased the amount of money required for cessation of drinking also increased.

In another manipulation, using the same two subjects and the same paradigm, the time when they were paid for abstaining was varied. Earnings were recorded on their earning sheet from 0 to 20 days after the money was earned. The subjects were told before they drank when the money would go on their record. The results suggested that the longer payment was delayed the more likely the alcoholic was to drink. This trend was revealed despite numerous other sources of variability which could have contributed to their drinking besides the delay in payment.

A series of four experiments with eight gamma alcoholics was conducted using a within subjects experimental design to further analyze the effect of programmed consequences on alcoholics' drinking. Periods in which there were scheduled consequences for excessive drinking were alternated with periods in which there were no scheduled consequences for excessive drinking. When excessive drinking resulted in the cancellation of most of the privileges of the program, the alcoholics drank up to 5 ounces and stopped.

Five gamma alcoholics had access to 24 ounces of 95 proof ethanol each weekday for five successive weeks (Cohen, Liebson, Faillace and Allen, 1971). There were differential consequences for moderate and excessive drinking during the first, third, and fifth weeks of the study. These weeks are referred to as the contingent weeks because access to privileges was contingent on moderation. During the contingent weeks if the alcoholic drank 5 ounces or less he maintained the privileges of the enriched environment. The enriched environment consisted of social, recreational and work privileges as well as a more palatable diet. If the alcoholic drank more than 5 ounces of alcohol per day, he could continue to drink up to 24 ounces of alcohol, but the privileges of the enriched environment were revoked for periods of 24 to 48 hours. During this period the alcoholic was required to remain in his bedroom. He could not work, socialize with staff, or enter the dayroom, and his food was puréed. The loss of privileges was referred to as the impoverished environment.

The second and fourth weeks of the experiment were non-contingent weeks. There were no differential consequences for moderate and excessive drinking. That is, no matter how much a subject drank (0 to 24 ounces of alcohol) he remained in the impoverished environment.

A typical subject's drinking during each day of the five week experiment is shown in Figure 1. The figure shows that the alcoholic subject drank moderately during the contingent weeks, and drank excessively during the non-contingent weeks.

This procedure was replicated with four other subjects and the results were similar. The average amount consumed during the contingent and non-contingent weeks by five alcoholic subjects is shown in Figure 2.

A *t*-test performed on the differences between the mean amounts of ethanol that each of the five subjects drank during the contingent and non-contingent weeks yielded a

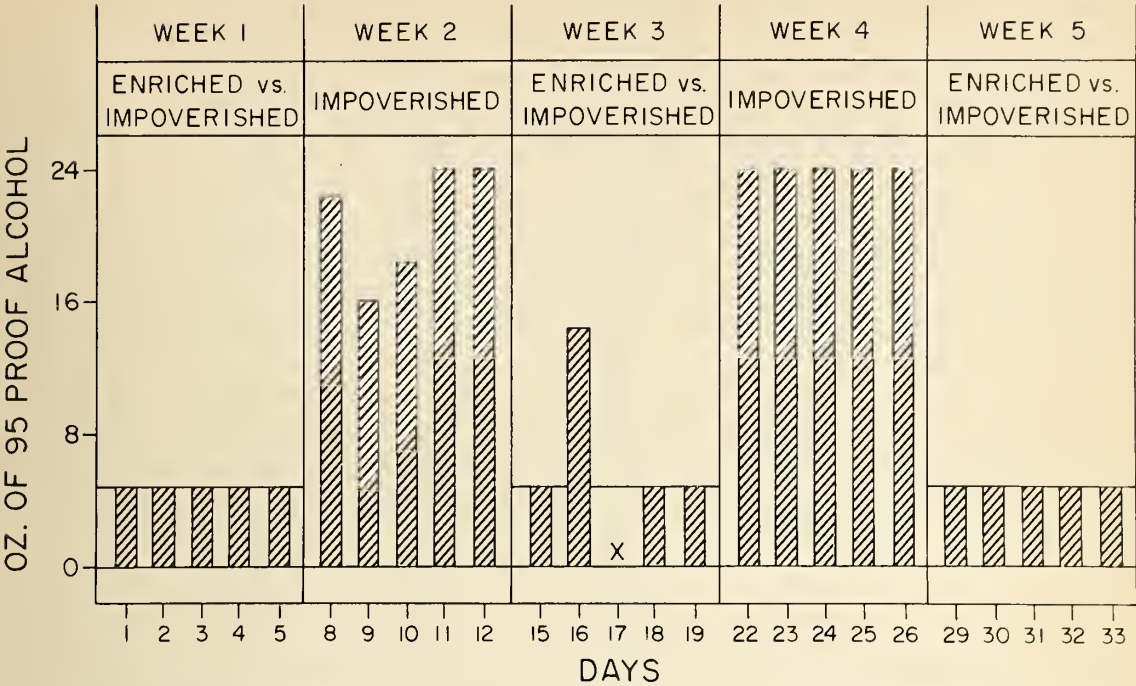


Figure 1. Number of ounces drunk each day during the contingent and non-contingent weeks.

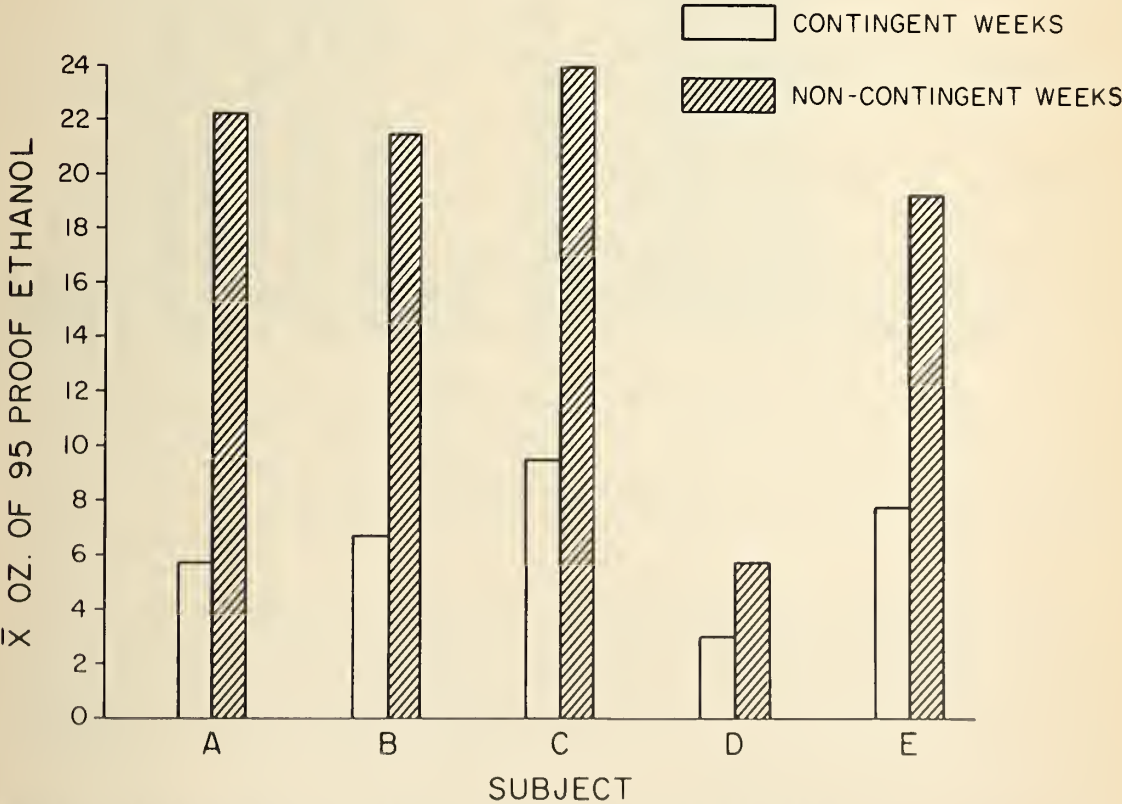


Figure 2. Mean number of ounces that 5 subjects drank during the contingent and non-contingent periods.

value of 3.47, which with four degrees of freedom is significant beyond the .05 level.

In the next experiment in the enriched-impoverished series, the first, third and fifth weeks of the experiment were identical to those just described (Cohen, Liebson, Faillace, and Allen, 1971). That is, if an alcoholic drank five ounces or less, he remained in the enriched environment. If the alcoholic drank more than five ounces he was in the impoverished environment for the remainder of the day he drank, plus the next day.

The conditions during the second and fourth weeks of the experiment, the non-contingent weeks, differed from the experiment just described. The subjects were in the enriched environment no matter how much they drank during the non-contingent weeks. In the previous experiment they were in the impoverished environment during the non-contingent weeks.

Four of the five who participated in the last experiment were the subjects in this experiment. A subject's drinking during each day of the experiment is shown in Figure 3. It is the same subject whose results were shown for the experiment just described. The alcoholic drank moderately during the contingent weeks, and excessively during the non-contingent weeks.

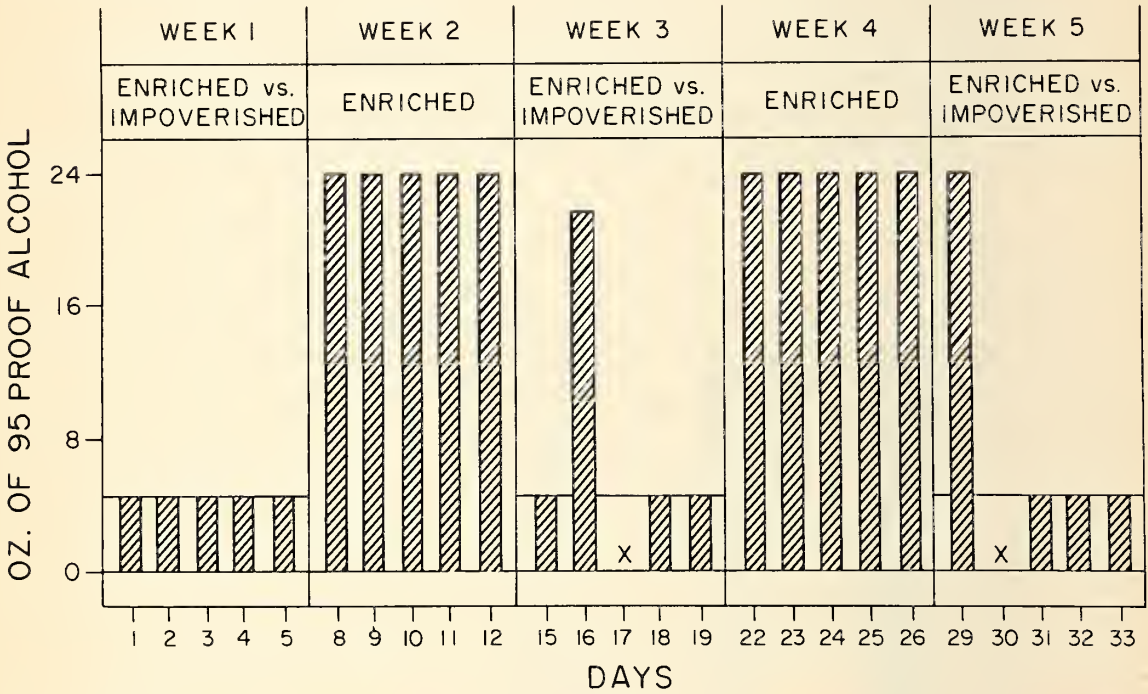


Figure 3. Number of ounces drunk each day during the contingent and non-contingent weeks.

The procedure was replicated with three other subjects and the results were similar. The mean amount consumed during the contingent and non-contingent weeks by four alcoholics is shown in Figure 4. A *t*-test performed on the differences between the mean amounts of ethanol that each of the four subjects drank during the contingent and non-contingent weeks yielded a value of 15 which with three degrees of freedom, is significant beyond the .001 level.

In Figure 5 the data from Figures 1 and 3 are juxtaposed for the sake of comparison. The point of interest in comparing these two graphs is the alcoholic's drinking during

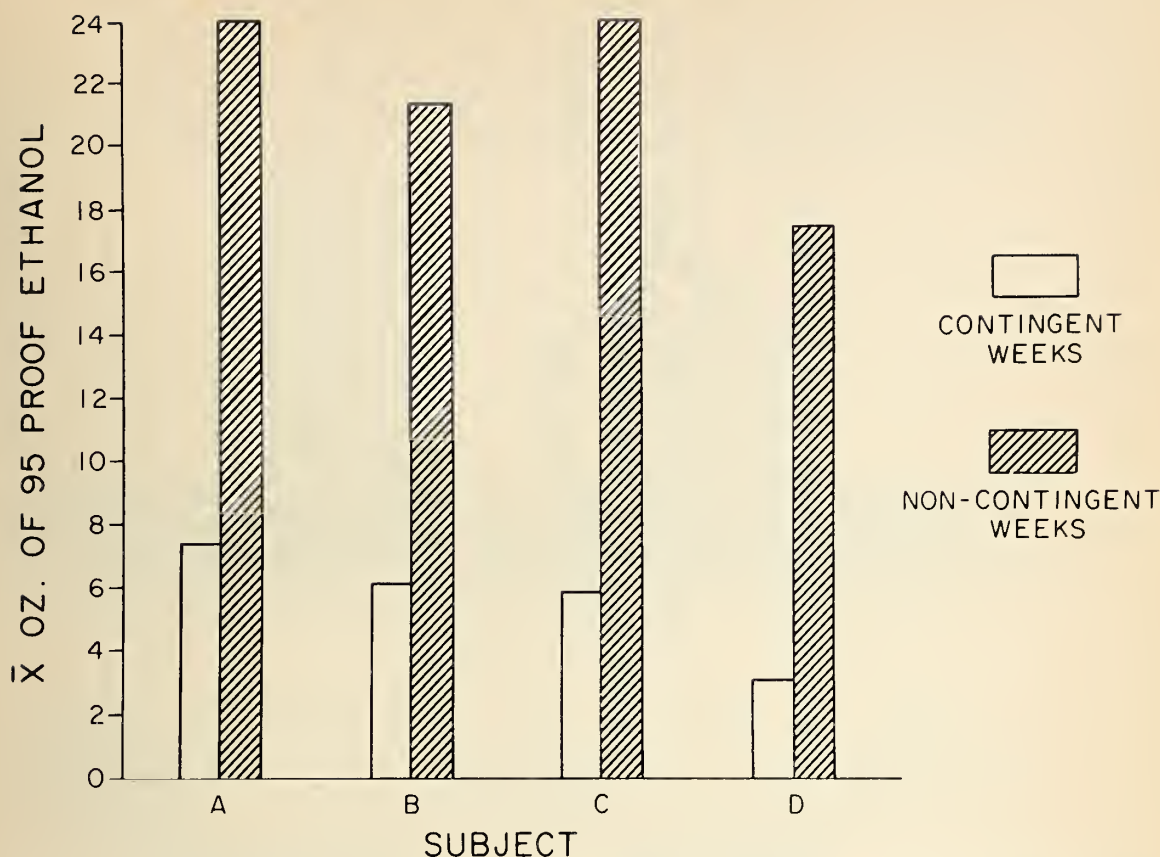


Figure 4. *Mean number of ounces that 4 subjects drank during the contingent and non-contingent periods.*

the non-contingent weeks (weeks 2 and 4). In the top graph, in the non-contingent weeks, the subject was impoverished no matter how much he drank. In the bottom figure, in the non-contingent weeks, the subject was enriched no matter how much he drank. In both cases he drank most of the alcohol available to him. The results indicate that drinking was curtailed when there were differential consequences immediately following it; and that the general quality of the environment in which the alcoholic was living did not affect drinking.

In another experiment in this series, the same contingency for moderate drinking was in effect for five successive weeks (Cohen, Liebson, and Faillace, 1971). If the alcoholic drank moderately he remained in the enriched environment and if he exceeded the 5 ounce limit he was impoverished for 24 to 48 hours. The one alcoholic to whom the contingency was applied drank moderately on all but two occasions during the 5 week period. (Figure 6.)

In the final experiment in this series the enriched-impoverished contingency was in effect for from 14 to 17 consecutive days including weekends, for three subjects (Cohen, Liebson and Faillace, 1973). Alcohol was continuously available in this experiment since it was thought that the opportunity to drink through the weekends, as the alcoholic does during a binge, might reduce the effectiveness of the contingency for moderation. However, it did not. Figure 7 shows that three alcoholics drank 5 ounces or less as long as the contingency was in effect. These three subjects had not participated in any of the previous experiments.

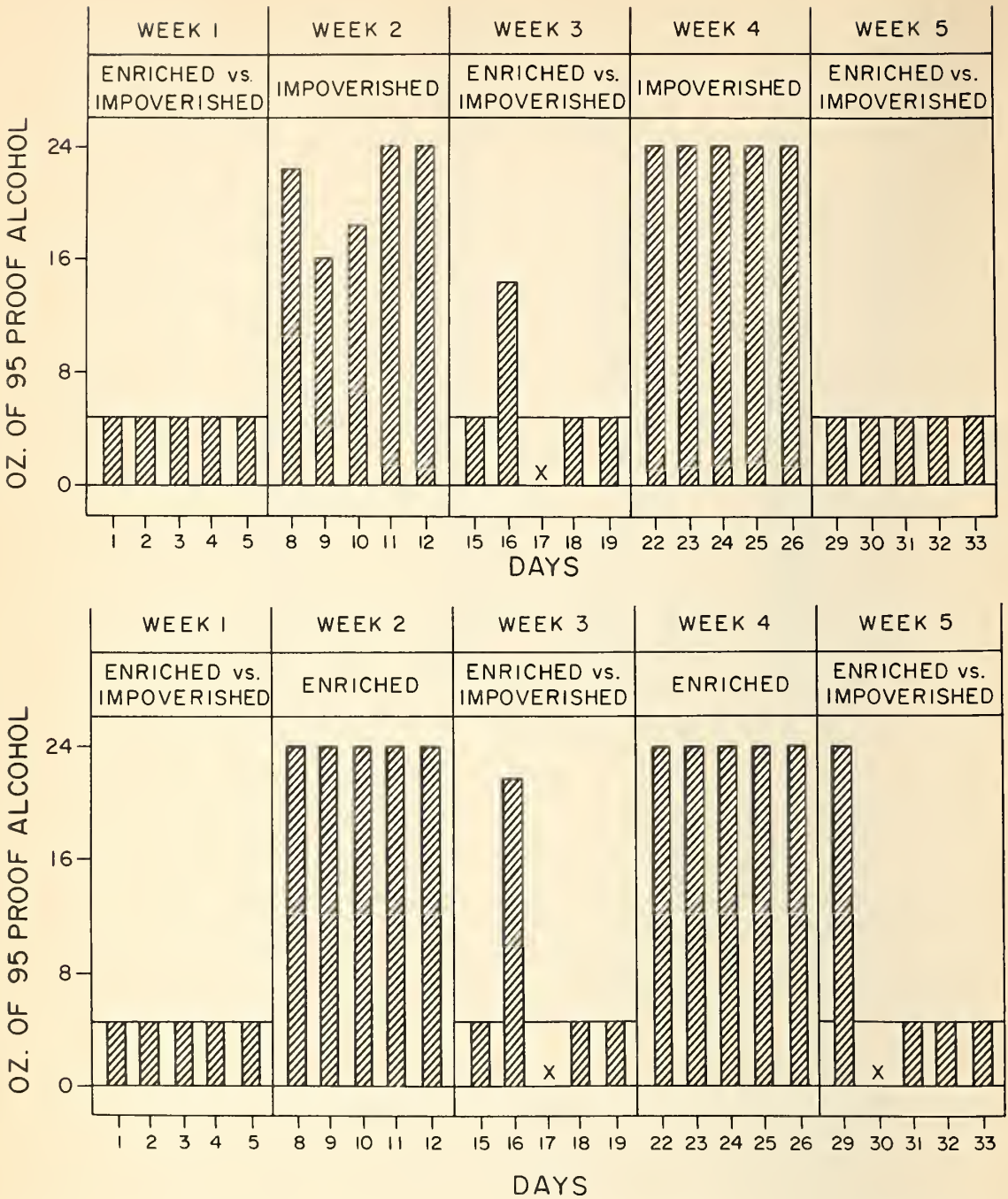


Figure 5. A comparison of number of ounces drunk during the non-contingent impoverished weeks and the non-contingent enriched weeks.

The results of this series of experiments in which there were differential consequences for moderate and excessive drinking indicate that gamma alcoholics can control their drinking for several weeks at a time when this behavior is differentially reinforced. The data also indicate that alcoholics will drink to excess if there are no immediate negative consequences for excessive drinking.

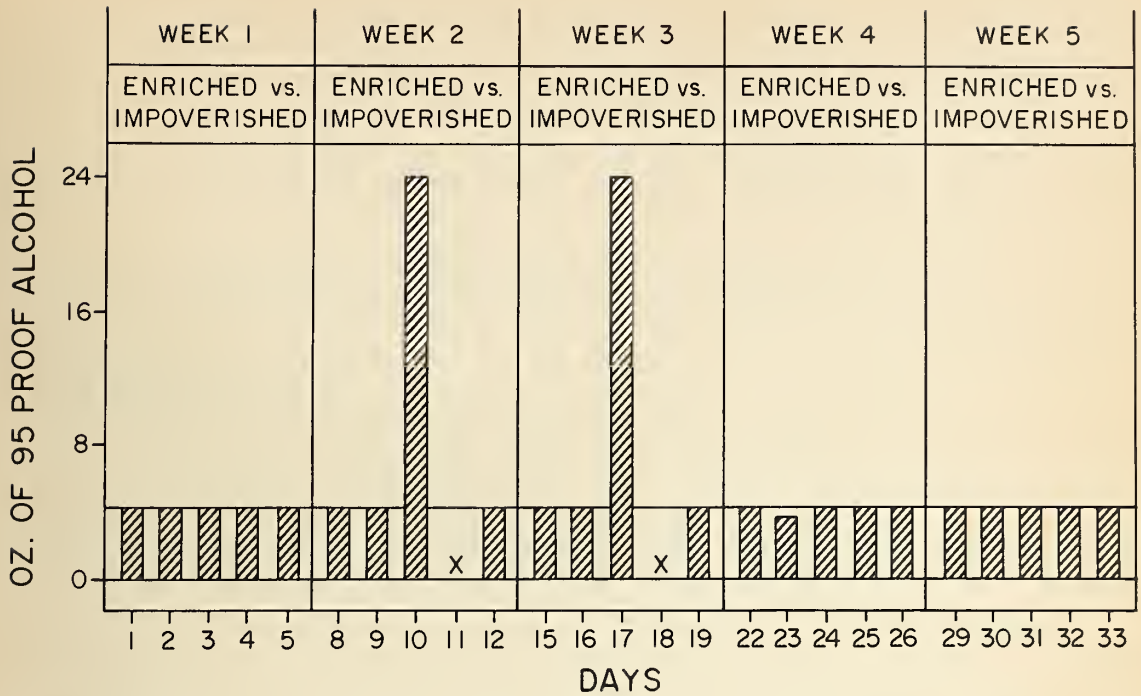


Figure 6. Number of ounces drunk each day during 5 consecutive contingent weeks.

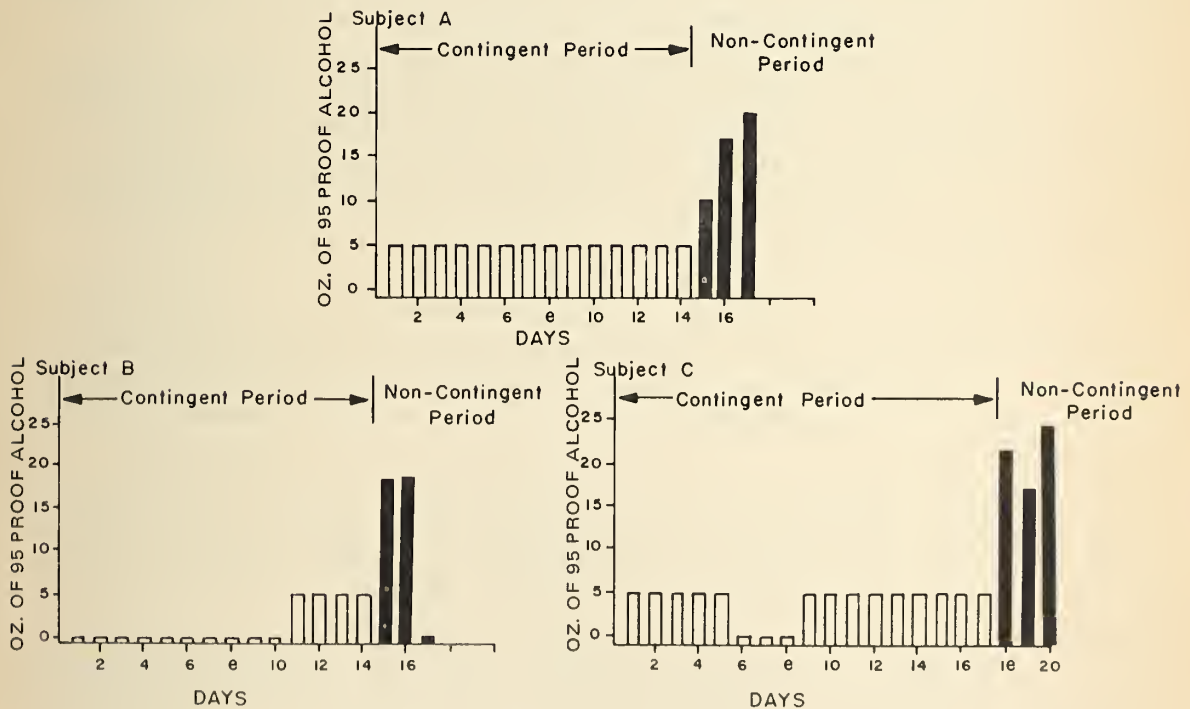


Figure 7. Number of ounces drunk each day during the contingent and non-contingent period.

Brief periods of social and physical isolation following each drink is another contingency which has been effective in suppressing gamma alcoholics' drinking (Bigelow,

Liebson and Griffiths, 1973). Ten alcoholics living on a hospital ward were given daily access to large quantities of alcohol (between 12 and 24 ounces of 95 proof ethanol). An A-B-A experimental design was used. During the A phases there were no scheduled consequences for drinking. The alcoholic could do as he wished after he obtained his drink. During the B phase each drink was followed by a 10 minute period of isolation. Isolation consisted of sitting in a telephone booth-like structure where only drinking and smoking were permitted.

During the two baseline periods, subjects consumed 95 per cent and 92 per cent of the drinks. During the contingent isolation phase subjects consumed 52 per cent of the available alcohol.

Shock was administered to nine alcoholics in a simulated bar setting in the hospital, for drinking the wrong kind of drinks (straight, rather than mixed) and for drinking too many drinks, too fast (Mills, Sobell and Schaefer, 1971). The subjects avoided shock if they drank mixed drinks, stopped after three drinks, and sipped their drink.

By the 13th and 14th drinking sessions in which shock was administered or threatened, the nine alcoholic subjects rarely exceeded the three drink limit, rarely ordered straight drinks, and sipped their drinks more often than they gulped them.

Sobell and Sobell (1972, 1973) administered behavior therapy concurrently with shock contingent on excessive drinking to 35 alcoholic voluntary admissions to Patton State Hospital. The behavior therapy was conducted during the drinking session in a simulated bar or home setting. Fifteen subjects were shocked for drinking any drinks, and twenty were shocked for drinking inappropriately (exceeding three drinks, ordering mixed drinks, and drinking more than one-sixth of their drink at a time).

There was a total of 17 sessions. In the first two videotaped sessions the alcoholic subject could drink up to 16 ounces of alcohol. No shock was used in these two sessions. During the third session no alcohol was available and the procedures to be used in all subsequent sessions were explained to each alcoholic. In the fourth through the sixteenth session, 6 ounces of 86 proof liquor were available for each 1½ hour session. Shock was applied for excessive drinking in sessions 4-7, 9-11 and 13-15. No shock was threatened or applied in sessions 8, 12 and 16.

The contingency for suppressing drinking was shock delivered on a VR 2 schedule (variable ratio schedule — on the average one out of every two drinking responses was shocked) when the alcoholic had exceeded the drink limit. Shock was one second in duration for ordering too many drinks and it was continuous for drinking drinks which exceeded the limit.

Punishable responses for those being taught to abstain were ordering or drinking any drinks. Punishable responses for those being taught controlled drinking were ordering straight drinks, taking too large a sip of a drink, allowing less than a 20 minute interval between drinks, and ordering more than three drinks per session.

The behavior therapy during the drinking sessions included videotape playback of drunken comportment, explanation of drinking as learned behavior governed by its consequences, a planned failure experience with an analysis of the alcoholics' reaction to it, and stimulus control analysis. This analysis consisted of identifying setting events for drinking and generating, evaluating and practising alternative responses to these events.

The 15 subjects who were shocked for any drinking drank only 6 per cent of the total drinks available to them during the 16 drinking sessions. They did not drink significantly more during the three probe sessions, in which no shock was administered, than

they did during the ten sessions in which the threat of shock was present. Thus it is not clear whether the threat of shock produced the large suppression of drinking for this group of subjects.

The 20 subjects who were shocked for inappropriate drinking made significantly more appropriate drinking responses in the sessions in which shock was threatened, than in the probe sessions when shock was absent. Shock had a significant suppressive effect on drinking for this group of subjects.

It is not possible to determine the contribution of the combination of behavior therapy procedures in addition to shock to the suppression of drinking; to determine the relative contribution of shock and behavior therapy these two procedures would have to be administered separately.

The use of two procedures concurrently — shock to suppress drinking, and behavior therapy to generate alternative responses to situations which have in the past set the occasion for drinking — reflects an assumption about the conditions that will suppress drinking. Most therapists assume that an alcoholic's drinking will more likely remain suppressed if the individual can make a response other than drinking, which will be reinforced in situations that have in the past precipitated drinking.

FACILITATING ALCOHOLICS' PROSOCIAL BEHAVIOR

Three behaviors which may compete with alcoholics' excessive drinking are social drinking, socializing and work. Procedures for instating social drinking have already been described, but the rationale for offering this therapeutic goal to alcoholics will be considered further since it is such a controversial issue in alcoholism treatment. Procedures for facilitating socializing and working in residential treatment programs have not been systematically explored. However an experimental analysis of these three classes of behavior suggests procedures which might be useful for inducing them.

Social Drinking

The promotion of social drinking as an appropriate treatment goal for alcoholics is a controversial issue which has received renewed attention in the past few years. It is a goal which can be defended conceptually, clinically and practically.

Conceptually, drinking is behavior which is subject to all the same laws that govern other behaviors. There is no evidence that it is easier, more efficient, or more desirable for the alcoholic to eliminate drinking from his or her repertoire than to bring it within socially acceptable limits. Despite the claims of Alcoholics Anonymous that the first drink results in a loss of control, there is substantial evidence to the contrary. Many specialists argue that to propose any goal other than abstinence is "unwise and dangerous" (National Institute of Mental Health, 1969, p. 37). However, the evidence to date strongly suggests that moderate drinking and abstinence are both attainable goals for the alcoholic and the choice should be a matter of individual preference.

Clinically, there are field studies, a laboratory study with extensive follow-up, and a case report which provide evidence that alcoholics return to social drinking in their natural milieu. In a large group of field studies conducted by several different investigators 12.5 per cent of a population of 2,461 alcoholics surveyed had returned to normal drinking 6 months to 8 years after having been diagnosed as alcoholic (Bailey and Stewart,

1967; Cain, 1964; Davies, 1962; Gerard and Saenger, 1959; Gerard, Saenger, and Wile, 1962; Gerard and Saenger, 1966; Kendell, 1965; Lambert, 1964; Moore and Ramseur, 1960; Morsier and Feldman 1952; Norvig and Nielsen, 1956; Pattison, Headley, Gleser, and Gottschalk, 1968; Pfeffer and Berger, 1957; Selzer and Holloway, 1957; and Shea, 1954). The conditions which resulted in a return to normal drinking were not known. It is not clear that this is the percentage of the alcoholic population who do return to controlled drinking. Reports alcoholics give to researchers about their drinking following treatment may be a function of the questions asked during the follow-up interview, the expectancy of the person conducting the interview, and the convictions about controlled drinking held by the therapist who treated the alcoholic. If social drinking has not been considered in therapy as an acceptable treatment goal, the alcoholic may not report it, since he or she may believe that such behavior is evidence of therapeutic failure. Gerard and Saenger (1959) found that in some clinics no alcoholics reported normal drinking after treatment while in others a consistent percentage of alcoholics reported normal drinking.

The Sobells' treatment program, described earlier, indicates some conditions which resulted in alcoholics' returning to controlled drinking. Information regarding the alcoholics' drinking following discharge was obtained from the alcoholic and friends, relatives and/or acquaintances familiar with his drinking, by phone and personal contact every 3 to 4 weeks for 6 months following treatment. Subject's drinking was classified into the number of days on which the subject was (a) abstinent, (b) drinking in a controlled manner, (c) drunk, or (d) incarcerated. Controlled drinking was defined as any day on which the subject drank 6 ounces or less, or any isolated 1 or 2 day sequence when between 7 and 9 ounces were consumed.

Both groups, those taught to abstain and those taught to drink in a controlled manner, drank moderately or abstained 65 per cent of the time in the 6 months following treatment. However, there was a difference in the number of days that the two groups of subjects were abstinent and drank in a controlled manner. Those taught to abstain drank moderately only 2.87 per cent of the time. Those taught to drink in a controlled manner did so 27.33 per cent of the time. These results suggest that when controlled drinking is sanctioned and taught to alcoholics, this behavior is maintained after the contingencies are no longer in effect. It is not clear whether it is the sanctioning of controlled drinking, the teaching of it or both which result in controlled drinking.

There is one clinical case report in which a problem drinker's drinking has been brought within socially acceptable limits with the use of contingency management procedures. Miller (1972) arranged a contract between a man and his wife which was designed to reduce the man's drinking. He was to pay her if he drank excessively and she was to pay him if she nagged him about his drinking. During a two week baseline period it was established that the problem drinker had a mean daily consumption of 7 to 8 drinks. The goal was to limit his drinking to three drinks per day which he would take before the evening meal. If he drank at any other time or exceeded the three drink limit he was required to pay his wife \$20.00 which she was to spend frivolously. She was also to ignore her husband when he exceeded the drink limit. She was to pay him \$20.00 if she nagged him about his drinking. He also was to ignore her nagging. Both husband and wife were to provide increased attention to the other for limited drinking and non-critical comments. The problem drinker incurred 8 fines during the first 11 days that the contract was in effect, and incurred no further fines for 20 consecutive days. After 6 months had elapsed a 10-day follow-up period was conducted and on all 10 days the subject drank 3 drinks or less. The authors do not say what effect this contract had on nagging.

Practically, a goal of social drinking may draw more alcoholics into treatment; it may induce them to remain in treatment; and it may be an easier goal for them to achieve than abstinence.

Alcoholic patients often seek help, but do not make a sustained effort to resolve the problems which caused them to seek help. Gerard and Saenger (1966) found that from a total of 789 patients in 8 outpatient alcoholism clinics, 410 (51%) dropped out by the end of the fourth interview. Panepinto and Higgins (1969) found that 51 per cent (40) of a group of alcoholic patients dropped out of treatment by the end of the second interview. Chafetz, Blane, Abram, Goiner, Lacy, McCourt, Clark and Meyers (1962) found that 75 per cent of 100 new patients at an outpatient alcoholism clinic dropped out by the end of the second interview.

When alcoholics drink, they often drop out of treatment. Pisani (1968) compared 16 alcoholics who remained in group therapy with those who dropped out and found that alcoholics who dropped out of treatment drank more during treatment than those who continued in treatment. Gerard and Saenger (1966) found that alcoholics who became controlled drinkers had significantly less contact with the clinics than alcoholics who became abstinent. Thirty-five per cent of 78 alcoholic patients who became abstinent maintained persistent (11 or more visits) contact with the clinic and only 17 per cent of 35 alcoholic patients who became controlled drinkers maintained persistent contact with the clinic.

Alcoholics may prefer moderation to abstinence and it may be easier to acquire a preferred behavior. When 19 alcoholics had the choice of fulfilling a contingency requirement by drinking moderately or abstaining, they drank moderately 76.6 per cent of the time and abstained 13.7 per cent of the time (Bigelow, Cohen, Liebson, and Faillace, 1972).

It may be that many alcoholics perceive drinking and participation in treatment as incompatible, because so much emphasis in the treatment setting has been placed on the achievement and maintenance of abstinence. The presence of alcohol in the treatment setting may help the alcoholic to learn that drinking is a choice that he or she makes and that drinking and participation in treatment are not necessarily incompatible. The presence of alcohol in residential treatment programs may also help the alcoholic to perceive treatment as being more directly related to his or her drinking problems which in turn may result in more regular participation in treatment — a necessary prerequisite to any therapeutic venture.

Socializing

The social facilitating effects of alcohol are common knowledge. Many persons, when they drink, become euphoric and experience a sense of well being, sociability, and temporary adequacy (Kittrie, 1973). In behavioral terms, we say that alcohol derives a substantial part of its reinforcing properties from its effect on selected aspects of the alcoholics' behavioral repertoire. There is a small body of evidence which suggests that for many alcoholics, alcohol alters interpersonal behaviors.

Researchers have observed changes in alcoholics' social, assertive, and aggressive behavior under controlled conditions. Doctor and Bernal (1964) observed 23 male and female alcoholics during five 45-minute individual psychotherapeutic interviews. Prior to the interview, each alcoholic received an intravenous infusion of 60 to 70 cc of 95 proof

alcohol. The investigators found that the alcoholics talked more freely and expressed more relevant emotions, especially hostility and guilt when they drank. Feinstein and Tamerin (1972) also found that one male alcoholic expressed more dynamically laden materials during the psychotherapeutic interview when he was drinking.

Diethelm and Barr (1962) observed two alcoholic men who drank for 14 successive days in a hospital. When sober the alcoholics were uncommunicative. When they drank they talked extensively and spontaneously and were demanding and assertive with each other and with the investigators.

McGuire, Stein and Mendelson (1966) observed 4 alcoholic men drinking up to 30 ounces of alcohol per day for 14 successive days in a hospital. Observations of their behavior were made by psychiatrists during daily 40 minute individual interviews and during 1 to 2 hour daily observation periods on the ward. The alcoholics were passive and compliant before the drinking began. During the drinking period there was an increase in socializing with women patients and staff, but not with men. Mayfield (1968a) also reported that alcoholics felt more friendly when they were drinking.

Bigelow (1973) has quantified the phenomenon of increased social interaction by alcoholics during drinking. The experimental procedure was to make alcohol available to alcoholics in a residential research setting over 10 days and compare their rate of social interaction on drinking days with their rate of social interaction on an equal number of non-drinking days. The availability of alcohol on a particular day during this 20 day period was determined by the roll of dice. On drinking days a maximum of 12 drinks was available. Subjects' behavior was recorded at random intervals throughout the day. When the timer sounded, staff would record whether a subject was awake or asleep, and if he was awake whether he was interacting socially or not interacting socially. Bigelow found that patients interacted socially 11 per cent of the time on non-drinking days and 39 per cent of the time on drinking days. This relationship has been observed with 5 alcoholic subjects. The increase has been from a 1.4 fold to a 6.0 fold increase.

Van der Spuy (1972) administered the Willoughby neuroticism scale 2 times to 40 male hospitalized alcoholics; once when they were sober and once after they had drunk 6 to 8 ounces of brandy. Their answers to questions about social contact were significantly different when they were sober from when they were drinking. During drinking they reported significantly less stage fright, less worry about humiliating experiences, that they were more in the foreground on social occasions, less shy, more likely to participate in a class discussion and/or debate, and that they had fewer feelings of inferiority.

Observations that interpersonal behaviors such as assertiveness, aggressiveness and amount of interpersonal contact are modified when alcoholics drink do not seem very startling. However, this information has not been used to design a treatment program for alcoholics.

An experimental analysis of the problem suggests a procedure that could be used to help alcoholics facilitate their social behavior. Alcohol could be used to induce the desired behavior change and the therapeutic environment could be arranged to maintain these behaviors while gradually reducing the alcohol dose over several treatment sessions. If the alcohol-facilitated behavior began to disintegrate because there had been too abrupt a change in the alcohol dose, the rate at which the dose was reduced could be adjusted. Artificial reinforcement could be introduced to maintain the social behavior during the transition phase until it was maintained by the reinforcers in the natural milieu.

The hypothesis that people drink to alter selected aspects of their behavioral reper-

toire has an advantage over the tension-reduction hypothesis which holds that alcoholics drink to reduce tension. The differences in behavior when the alcoholic is sober and drunk can be observed. Those behaviors which occur when the alcoholic is drinking are behaviors in which he or she wants to engage. Procedures can be developed to facilitate the alcoholic engaging in those behaviors without alcohol. Although this will be a delicate clinical procedure it deals with observable behaviors, and the therapist can objectively determine whether the desired behavior has been acquired.

Work

Another behavior which for some alcoholics may compete with drinking is work. The major purpose of any residential treatment program for alcoholics should be to provide an environmental support system that systematically and frequently reinforces two classes of behavior — the choice to remain sober when alcohol is readily available, and the choice to engage in behaviors which, when sufficiently reinforced in the natural milieu, may compete with drinking. Work is one such behavior and instating or reinstating working behavior is often a problem in long term residential treatment facilities for alcoholics. Work could be systematically reinforced with an improved standard of living within the residential treatment program which would include increased access to the goods, services, and privileges of the program. Drinking and/or other self-destructive behavior should result in the loss of status but not discharge from the program.

CONCLUSIONS

It is often argued that alcoholics have multiple problems; that drinking is only one of them, and that drinking will not be suppressed unless the other problems are resolved. Conversely, it is possible that curtailing or eliminating drinking may have favorable effects on other areas of functioning. However, eliminating one behavior does not guarantee that more constructive alternative behaviors will take its place. Thus, if the alcoholic has multiple behavioral deficits, procedures to foster other more adaptive behaviors must be employed for each particular behavior to be instated, whether it be interpersonal or vocational skills, or avoidance of other drugs. However, attention to these problems should not preclude the application of procedures required to control drinking.

Two critical features of a procedure aimed at curtailing drinking are frequent monitoring of alcohol ingestion and/or blood alcohol concentration levels and systematic programming of incentives for sobriety. Correct timing and regularity are crucial aspects in determining the efficacy of incentives.

It is often argued that reinforcement procedures will not work for alcoholics. The reasoning is, that the alcoholic has had many incentives to remain sober, and continued to drink despite the losses that his or her drinking incurs. However, the natural reinforcers for sobriety and punishments for excessive drinking are often remote and are delivered on an irregular schedule. It may be the lack of immediacy and certainty which weakens their efficacy. A residential treatment program should be engineered to counteract the inadequate schedules of reinforcement present in the natural environment for achieving the desired behavior — sobriety.

All forms of treatment for alcoholics have as their aim the reduction of drinking, but the procedures used to pursue this goal vary considerably. The development of behavioral treatment approaches in the field of alcoholism is one aspect of a more general and very active trend concerned with the application of the principles and techniques of operant

psychology to clinical problems. This approach is dedicated to the development of procedures which remove the troublesome symptom. In some respects this trend parallels developments in medicine in which all-purpose therapies of limited efficacy have been replaced by powerful specific procedures designed to treat particular physical disorders (Bandura, 1967).

A behavioral conceptualization of alcoholism has resulted in the specification of treatment goals in objective quantifiable terms and the development of treatment procedures which can be evaluated in terms of their effectiveness in achieving these goals. New treatment goals and procedures for alcoholics have also been suggested as alcoholism has been defined in behavioral terms.

Several experiments with alcoholics in residential research programs in which alcohol has been readily available and the consequences of drinking have been programmed in such a way as to reduce the probability of drinking, are reviewed in this paper. The results of this research indicate that alcoholics' drinking can be partially or fully suppressed by the appropriate programming of environmental consequences and these findings have implications for the design of residential treatment programs for alcoholics.

The availability of alcohol in the treatment setting is a prerequisite for determining the conditions under which the alcoholic drinks or abstains and for determining the differences in the alcoholic's behavior when he or she is drunk or sober. Since information on both of these variables is very important in the design of a treatment program, a strong case is made for incorporating alcohol into residential treatment programs for alcoholics.

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The Need for Realism, Relevance and Operational Assumptions in the Study of Substance Dependence

Mark B. Sobell and Linda C. Sobell¹

INTRODUCTION

This presentation attempts to elucidate certain general issues which we believe warrant serious consideration by all substance dependence researchers at this time. The three areas chosen for emphasis, while independent in many respects, share a common underlying theme. This theme suggests that an applied research orientation to substance dependence should take some priority over basic research which is oriented toward developing comprehensive theories of etiology. In this paper we focus primarily on *alcohol dependence* as an example of substance dependence. Of course, care should be taken when generalizing specifics from alcohol dependence to other types of substance dependence.

OPERATIONAL ASSUMPTIONS

Consequences of Theorizing Without a Data Base

The various approaches to the construction of theories of etiology in the field of alcohol dependence whether scientific or para-scientific all suffer from a paucity of supporting objective evidence. Nevertheless, professionals and laymen alike often accept a certain approach as an axiomatic and cherished belief. The evidence supporting this statement will not be reviewed here, as others (Keller, 1972b; Cain, 1964; Jellinek, 1960; Pattison, 1969) have already summarized the evolution of the various theoretical positions.

¹Orange County (California) Department of Mental Health, Alcoholism Services and University of California, Irvine.

Most of the existing theories can be characterized as representing one or the other side of a biological-psychological schism. Typically, each position professes to recognize alternative viewpoints but seldom makes any serious attempt to deal with evidence supporting them. Some of the most popular theoretical positions are those hypothesizing biological bases for alcoholism. Among the best known of these are Jellinek's 1960 exposition of the disease concept, and Williams' (1959) nutritional deficiency theory. Other major theoretical positions have advocated the importance of nurture in precipitating and maintaining alcohol dependence. Masserman and Yum (1946) provided some of the earliest evidence for such an approach, and their findings were later supported by Conger (1951). Later approaches have predominantly advanced operant learning theories (Narrol, 1967; Bandura, 1969; Sobell and Sobell, 1972).

The evolution of theories of the etiology of alcoholism has produced a host of advantages, typical of "school-type" theory advocacy. Perhaps primary among these advantages are the directedness and intensity of research which a theoretical framework generates. If a structural theory is basically sound, the resulting directed effort and the potential rapid advances in knowledge are valuable dividends from the energy invested. In addition to stimulating new research, the developing theory provides a framework in which to interpret the results of studies. What, however, are the consequences of such activities if the underlying structural theory is not ultimately validated?

Theoretical debates often create as many problems as they are meant to resolve. Overly strong identification with theoretical positions can metamorphize testable hypotheses into preconceptions in need of verification, thereby minimizing the attention given to negative or contradictory evidence. Further, there exists a danger of becoming so enmeshed in seeking or assuming proof for a theoretical position that other important issues are neglected. Also, since clinicians and researchers are generally viewed as credible and authoritative sources of information, what they describe as plausible hypotheses can be reified by others as documented facts. The evolution of the disease concept of alcoholism serves as a good example of such reification, not only by the general public, but by many professionals as well.

Around the turn of this century a group of physicians proposed that alcohol dependence be considered as a disease (MacAndrew, 1969). They were severely criticized and the proposition was for the time dropped. However, half a century later, the *Zeitgeist* had changed. A similar movement, led by Jellinek (1960), was eminently successful although there was little additional evidence to justify a disease conception. Keller (1972b), Robinson (1972), and others have reviewed the process by which the disease concept came of age. Three of their points are especially relevant to this discussion: (a) the disease concept was not based on hard scientific evidence, but rather on the self-reports of a selected population of highly identified recovered alcoholic members of Alcoholics Anonymous; (b) basically, it was a sociopolitical manoeuvre which has successfully fulfilled its intentions; and (c) while Jellinek viewed alcohol dependence as a possible disease, he did not consider the disease concept as a proven fact, and simply meant to point out that intense drinking problems had many associated disease processes. Nevertheless, it was decided (for what at the time were justifiable political reasons) to declare alcoholism a disease. Robinson (1972) considered in some depth the nature of the consequences of this reification of the disease concept of alcoholism. He concluded that the general acceptance of this ill-defined notion has probably led to the development of false expectations about the nature of alcohol dependence, its treatment and prognosis. In a fine and often overlooked article, Roman and Trice (1968) pointed out that the disease

concept has serious social labelling consequences. If "alcoholism" is a disease, then certain role expectations, derived from the cultural expectancies of "sick" or "ill" behavior, apply to the individual "alcoholic." They warned that in the absence of supporting evidence, the sick role assignment might even result in legitimizing deviant drinking patterns for individuals labelled as alcoholics. Thus, they cautioned that the disease model, "...has resulted in a labelling process that may in itself set the stage for the development of true alcohol addiction (p. 250-251)." Taking another tack, Verden and Shatterly (1971) argued that the disease concept has served useful personal functions for individuals working in the field of alcohol dependence, thereby possibly contributing to a general resistance of progress in understanding the compulsive drinker.

Pattison (1969) has summarized the original intent of the disease concept:

The major advantage of defining alcoholism as a disease is social. It legitimates social support for rehabilitation of the alcoholic rather than punishment. To say that alcoholism is an illness should not be construed as a statement about the etiology or treatment of alcoholism (p. 953-954).

Yet, in reality, the cautions originally intended for use with the disease concept are seldom recognized. Consider the following two examples which recently appeared in local newspapers. In the first article, a state senator was reported to have objected to legislative approval of a bill that would provide additional funds for alcohol rehabilitation programs on the basis that, "...such programs relied on 'psychological' techniques and (he) insisted that the only meaningful cure for alcoholism would be 'medication that has not been developed yet'." In the second example, the physician in charge of a newly established inpatient alcoholic rehabilitation program was reported to have some rather strong opinions. With respect to the appropriate treatment modalities for alcoholism, he stated, "Alcoholism is a disease and should be treated like other diseases — in a hospital." As for the variety of orientations included in his program, he stated that, "There is no treatment for alcoholism, other than permanent and total abstinence." These quotations are not cited to derogate individuals but simply to demonstrate that examples of this kind of reification are commonplace events, at least in the United States.

Other adverse consequences have resulted from an inordinate allegiance to this theory. Although sound scientific evidence for a disease conception is still lacking, some professionals in the field are well received for excoriating research on alternative viewpoints. An example of this kind of rigidity occurred recently at a major scientific conference. At that meeting, those few researchers pursuing alternative conceptualizations were derogated in the following manner: "Fortunately, these moralistic dogmatists are but a tiny minority in the field of alcoholology despite the large noise they produce" (Madsen, 1973). This type of contestation and excessive allegiance to theoretical positions does not encourage progress in the scientific study of alcohol dependence, nor does it encourage researchers to develop innovative approaches. To be sure, theoretical controversies which lack a data base and thus are in reality more a matter of conflict of beliefs are not restricted to the disease concept of alcoholism. However, the intensity of debate generated by this topic qualifies it as a superb example of such conflict.

Researchers concerned with other substance dependencies should carefully consider the history of alcohol dependence research, as there are valuable lessons to be learned. Over time, the political advantages gained from sacrificing scientific method seem to slowly erode when such concepts become accepted by the public, and by many professionals, as proven facts. Thus, the vicarious outcome of this process can serve to hinder

progress in developing efficacious treatment programs for the very individuals originally intended to receive the benefits of such political action. Surely there are many legislative options which could equally well accomplish the political objectives while avoiding compromise of scientific methodology and credibility. Fingarette (1970), writing from a legal viewpoint, expressed a similar opinion and caution: "...one tempting road to reform — the building of a new constitutional doctrine on the basis of purported medical knowledge of alcoholism — is also a very dangerous one (p. 812)."

Operational Assumptions: An Alternative

To avoid further inexpedient theoretical conflicts, we suggest an alternative mode of function which would allow us to capitalize on the advantages of theorizing with a minimum of discord. A prelude to the proposed resolution requires the introduction of a specially defined term, *operational assumptions*². The difference between *explicitly acknowledged* operational assumptions and theories of etiology about alcohol dependence, is not in the evidence for viewpoints, but rather in the manner with which those viewpoints are advocated. The difference involves the orientation and expectations of the researcher and of persons evaluating or studying that research. In making an operational assumption, one first *assumes*, for the purposes of directed research, that a certain state of affairs exists. Based on the logical implications of these assumptions, basic or applied research studies are then generated. In making operational assumptions, particularly those involving the formulation of treatment approaches, one purposely does not deal with matters of ultimate truth, but only with utility. This difference is not merely semantic frivolity. The field of alcohol dependence has been plagued with destructive controversy about the validity of theories, and with public and professional reification of theoretical elements. Clarifying the assumptive nature of the basis for research investigations can provide a permanent caveat against both reification and the need to corroborate one's own position at the sacrifice of objective evaluations.

While operational assumptions provide a formidable means of avoiding political and emotional invective, there are at least two additional reasons for advocating their use. First, it is quite possible that only limited *practical* consequences will result from discovering the "true" etiology of alcohol dependence. Knowledge of this etiology could be tremendously valuable in designing effective treatment and prevention programs. However, once alcohol dependency has become a self-destructive and relatively frequent pattern for an individual, the true etiology of that dependence will only be directly relevant to one aspect of the treatment. Once developed, alcohol dependence is a multi-faceted and highly complex syndrome. Thus, a synthesis of many orientations will be required in order to provide an effective and comprehensive treatment network. For instance, all of the following types of variables must be considered at some time: (a) biological variables — at a minimum, excessive alcohol consumption is related to various degrees of physical deterioration and disease processes; (b) environmental and psychological variables — alcohol is only available from the external environment, and the manner of drinking alcoholic beverages is learned; and (c) sociocultural variables — the drinking or non-drinking individual lives within a culture with certain societal norms. Thus, whatever the true etiology

²Readers may notice that "operational assumptions", as here defined are in many ways identical with the more familiar concept of "working hypotheses". The denotation, "operational assumptions", stresses that the involved relationships do not yet have a proven empirical basis, and that various operations are based on these presupposed relationships.

of alcohol dependence, a comprehensive treatment regimen must include elements to deal with the *disease complications*, *psychological complications*, and *social complications* of alcohol dependence. A simple analogy which appears in the novel, *The Terminal Man* (Crichton, 1973), makes a similar point quite succinctly: "A match may start a fire, but once the fire is burning, putting out the match won't stop it. The problem is no longer the match. It's the fire (p. 258)."

The second additional reason for advocating the use of operational assumptions is that it may be very premature at this time to attempt to develop comprehensive or valid theories of substance dependence. This suggestion is based on the premise that a large portion of the current basic science and experimental foundations for such theories are in a state of flux, themselves. While this relationship can be easily extended to many of what we will refer to as the reduction formulations³ (*i.e.*, biochemistry, neurophysiology, psychoanalytic theory, learning theory), we have chosen to present an example of this phenomenon from an area of study with which we are familiar. Thus, currently, it is unlikely to be profitable to pursue the formulation of a comprehensive and elaborate theory of alcohol or any other substance dependence as a learned operant or learning deficiency phenomenon. The reason for this conclusion is that fundamental learning theories have not yet reached a stable point of development. New information and concepts are constantly being advanced while old concepts are being modified. At this time, a realistic theoretical learning approach must embody a large amount of intrinsic flexibility in order to accommodate new developments and inter-disciplinary considerations. For example, reinforcement learning theory is currently besieged by a number of studies that appear to be more parsimoniously explained either by ethologically derived species-specific behavioral tendencies, by the informational function of stimuli rather than reward function, or by an expectancy — anticipation process (Seligman, 1970; Staddon and Simmelhag, 1971; Bolles, 1972; Garcia, Clarke, and Hankins, *In press*). As reinforcement learning theory metamorphizes to incorporate the parsimonious explanation of new phenomena, there is no way of accurately predicting what role will remain for "reinforcers" in such a theory.

We do not suggest that theoretical conceptualizations should be avoided, or that theorizing serves no purpose. However, it is important to keep the state of the art in perspective when attempting to develop comprehensive and verifiable theories. Such a perspective directs concentration of effort upon producing facts requiring explanation, rather than on defending controversial positions lacking substantive evidential bases. This argument is more cogent when considering disease-based theories, since disease-oriented research is one of the few areas where specific causal relationships have often been undeniably established between antecedents and consequents.

Summary of Operational Assumptions

In summary, it is suggested that researchers in the field of substance dependence explicitly acknowledge the theoretical foundations upon which they base their research to be "operational assumptions." The process of theory development can have multiple advantages, and from a political standpoint this certainly has been the case in the field of alcohol dependence. However, a rigid adherence to theoretical positions lacking a sub-

³In this passage, the term "reduction" is not meant to be used as typically defined by the philosophy of science. It is borrowed, for our purposes, to simply connote the underlying complex of principles accepted for information and explanation upon which the statement of a theory may be based.

stantive evidential base can produce disadvantages which exceed the benefits gained. It would be scientifically more defensible and advantageous for professionals to state directly that they are simply designing their work *as if* alcohol dependence were basically a disease process, learned phenomenon, or whatever. Emphasizing the assumptive nature of an investigation clearly communicates the non-definitive state of our present knowledge. The next section describes an example of research designed in accordance with operational assumptions.

The Use of Operational Assumptions: An Example

The following briefly summarizes an example of how one can use a theoretical perspective as the foundation for developing a treatment experiment, without first assuming the ultimate "truth" of that basic foundation. The experiment demonstrates that it is possible and relatively simple to design an alcohol dependence treatment evaluation experiment which adheres to the rather rigid demands of sound scientific methodology. While satisfactory use of the principles of experimental design is both an expected and frequent occurrence in basic research studies, controlled applied studies are rare in alcohol dependence research.

A few years ago, a treatment evaluation experiment was conducted at Patton (California) State Hospital (Sobell and Sobell, 1972, 1973c) and the results reported (Sobell and Sobell, 1973b, d). We will discuss only selected elements of that experiment here. As mentioned earlier, the experimental treatments were designed in accordance with implications of a "rationale" which had a theoretical foundation but which was not proclaimed as necessarily being "correct." The rationale used was that heavy, abusive, dependent drinking could be considered as a discriminated, operant response. Prior to the study, a review of existing evidence had suggested that the drinking behavior of alcohol-dependent individuals appeared to have characteristics typically descriptive of operant responses. Others had also noted these similarities (Lazarus, 1965; Mello and Mendelson, 1965; Bandura, 1969; Nathan, Titler, Lowenstein, Solomon and Rossi, 1970). The significance of the experiment conducted at Patton was that rather than performing basic research studies to further document the similarity between alcoholic drinking behavior and operant responses, some treatment implications of this conception were investigated and tested. Thus, alcoholic drinking was "presumed" to be a response which occurs in selective and definable situations and is acquired and maintained primarily as a result of its consequences. Among the treatment implications which can be derived from these assumptions are: (a) treatment sessions should include dealing directly with the behavior of excessive drinking; (b) whenever possible, treatment conditions should be designed to maximize generalization of the treatment effects; (c) if drinking is to be made a less probable response in certain stimulus situations, alternative methods of dealing with those situations (or training in alternative methods) should be provided for the patient; (d) an optimal treatment should take into account the learning history of each patient and specifically tailor the treatment to that individual; and (e) the treatment goals should be those most likely to be attained and maintained with respect to that individual's post-treatment environment.

The primary intention in designing a treatment program consistent with these implications was not to test an environmentalistic theory of the etiology of alcohol dependence, but to evaluate the effectiveness of a treatment design. The conventional state hospital alcoholic treatment program at Patton State Hospital served as a comparison

control treatment. Earlier work at this same facility had reported treatment outcome results similar to those found for other traditional inpatient programs (typically, between 20% and 40% success, evaluated by various criteria). An evaluative study seemed worthwhile, if only to improve upon this unflattering statistic.

Briefly, 70 hospitalized male, *gamma* alcoholics had volunteered to participate in the experiment. After receiving medical and psychiatric clearance, subjects were assigned to either a controlled drinking or a non-drinking treatment goal. Subjects were then randomly assigned either to an experimental group receiving 17 experimental treatment sessions or to a control group receiving only the conventional state hospital program. The experimental design, presented in Figure 1, traces the derivation of the four experimental conditions. This design can also be interpreted as two concurrent experimental treatments – non-drinking and controlled drinking goals – each with an appropriate control group.

The specific experimental treatment sequence is described in detail elsewhere (Sobell and Sobell, 1972). Briefly, the sequence included sessions where the patient became drunk in an experimental bar setting and was videotaped; self-confrontation with videotaped drunken behaviors; shaping of appropriate drinking or non-drinking behaviors as defined by the treatment goal; availability of alcoholic beverages during sessions; and "behavior change training sessions." Behavior change training sessions concentrated on determining subject-specific setting events for drinking, and training the subject to generate a series of possible alternative responses to those situations, to evaluate each of the

I.B.T.A. EXPERIMENTAL DESIGN

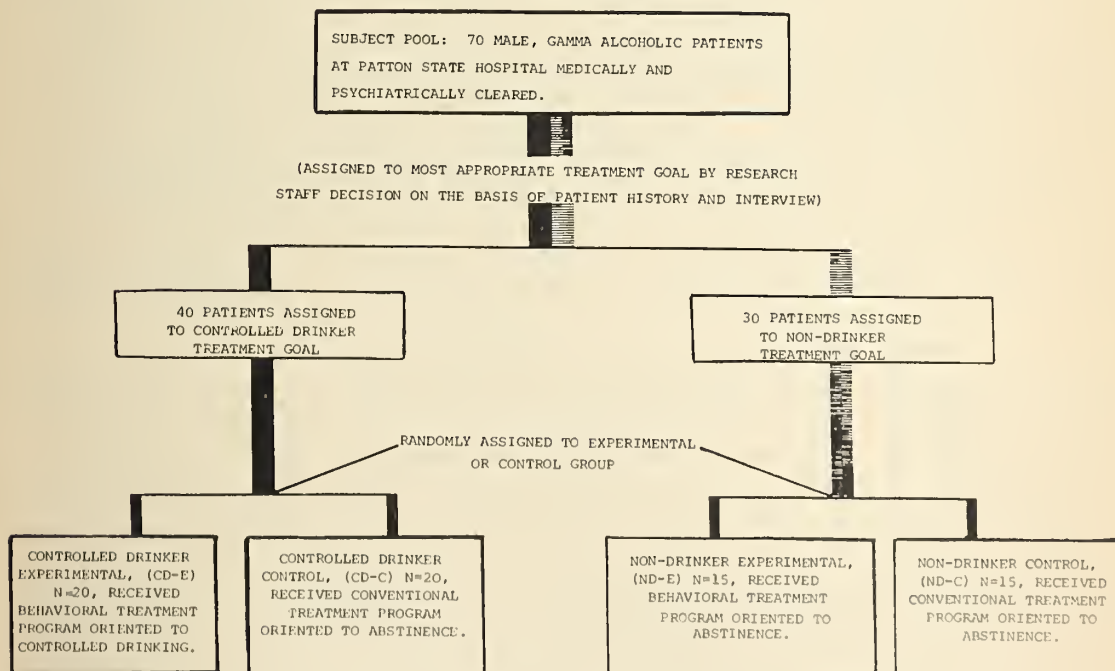


Figure 1. *Experimental design used in the Patton study. Figure adapted from Behaviour Research and Therapy, 11: 599-618, 1973. Permission granted by Pergamon Press Ltd.*

delineated alternatives for potential short-and long-term consequences, and to exercise the response which could be expected to incur the least self-destructive long-term consequences.

For a period of two years after hospital discharge, intensive follow-up was conducted on each subject. Both subjects and their collaterals were contacted every three to four weeks throughout the two-year period. The outcome results have been presented in extensive detail elsewhere (Sobell and Sobell, 1972; 1973b, c, d). Since many studies had already demonstrated that changes in drinking behavior are frequently, but not always, associated with changes in other aspects of life function (see review in Pattison, 1974. In press), eight dependent variable measures were used to measure treatment outcome. For sake of brevity, however, only results for the measure of drinking behavior will be discussed. Daily drinking disposition data were gathered at all follow-up contacts. This measure, new to alcohol dependence treatment outcome studies, represents a significant improvement over traditionally vague measures. Its advantages will be discussed later in this paper. In generating the measure, a subject's drinking disposition on any given day was categorized as either: (a) *abstinent* — no drinking; (b) *controlled drinking* — consumption of 6 ozs. or less of 86-proof liquor or its equivalent in alcohol content; (c) *drunk* — consumption of greater than 6 ozs. of 86-proof liquor or the equivalent in alcohol content; (d) *hospital incarceration* for alcohol-related health problems; or (e) *jail incarceration* for alcohol-related reasons. For evaluating results, abstinent and controlled drinking days are summarized as "functioning well," with remaining days summarized as "not functioning well."

Table I displays results for all experimental conditions for the first and second year of follow-up. Tests previously reported indicated that differences between the controlled drinker experimental and controlled drinker control groups were statistically significant for each of the four consecutive six-month follow-up intervals. However, differences between the two non-drinker groups were only statistically significant for the first year of follow-up. As with any outcome study, these results are susceptible to many interpretations. Our suggested interpretation, which is consistent with the concept of operational assumptions, is that some factor or factors included in the controlled drinking experimental treatment were effective in improving the post-discharge prognosis of a great many of those subjects. Further applied studies should attempt to replicate the findings and determine which of the experimental elements, alone or in combination, are effective.

It is not only unnecessary, but would be ill-advised, to conclude that a strict learning theory interpretation of the etiology of alcohol dependence is indicated by the above results. Instead, it is preferable to simply state that a treatment approach designed from the implications of an *assumption* that alcohol dependent drinking is a discriminated, operant response has yielded, in this first test, positive findings. This, in itself, is enough to warrant performing further tests, replicating and then sophisticating the approach. Moreover, these findings do not imply that one should cease searching for genetic or biologic determinants of alcohol dependence. In a like manner, should such determinants be found, there is no reason for treatment programs such as the one just described to be abandoned because of an incongruent theoretical orientation. It is reiterated that effective treatment of alcohol dependence may, in fact, turn out to be relatively independent of the etiology of that syndrome. For example, it is possible that the experimental treatment under discussion dealt effectively with the social complications of alcohol dependence, and perhaps that is why certain subjects functioned better than others after discharge.

TABLE I

TWO YEAR FOLLOW-UP RESULTS FOR SUBJECTS IN THE PATTON EXPERIMENT.

Group ^a	Measure		Year 1	Year 2
CD-E, N=20	<i>n</i> located for complete follow-up	:	20	19 ^b
	Daily drinking disposition —			
	Mean % of days abstinent	:	45.29	65.85
	Mean % of days controlled drinking	:	25.19	23.76
	(Total mean % of days functioning well=)	:	(70.48)	(89.61)
	Mean % of days drunk	:	14.02	7.87
	Mean % of days incarcerated in hospital	:	11.34	1.61
	Mean % of days incarcerated in jail	:	4.16	0.92
	Percentage of subjects found to be functioning well $\geq 80\%$ of all days	:	55.00	78.90
CD-C, N=20	<i>n</i> located for complete follow-up	:	19	18 ^c
	Daily drinking disposition—			
	Mean % of days abstinent	:	25.66	37.34
	Mean % of days controlled drinking	:	9.56	6.13
	(Total mean % of days functioning well=)	:	(35.22)	(43.47)
	Mean % of days drunk	:	49.88	48.36
	Mean % of days incarcerated in hospital	:	5.55	2.14
	Mean % of days incarcerated in jail	:	9.35	6.03
	Percentage of subjects found to be functioning well $\geq 80\%$ of all days	:	10.50	22.22
ND-E, N=15	<i>n</i> located for complete follow-up	:	15	13 ^d
	Daily drinking disposition—			
	Mean % of days abstinent	:	65.06	61.29
	Mean % of days controlled drinking	:	3.33	3.32
	(Total mean % of days functioning well=)	:	(68.39)	(64.61)
	Mean % of days drunk	:	13.99	18.85
	Mean % of days incarcerated in hospital	:	11.77	6.49
	Mean % of days incarcerated in jail	:	5.85	10.05
	Percentage of subjects found to be functioning well $\geq 80\%$ of all days	:	33.33	53.87
ND-C N=15	<i>n</i> located for complete follow-up	:	14 ^e	14 ^e
	Daily drinking disposition—			
	Mean % of days abstinent	:	32.35	43.62
	Mean % of days controlled drinking	:	6.13	1.56
	(Total mean % of days functioning well=)	:	(38.48)	(45.18)
	Mean % of days drunk	:	39.85	35.91
	Mean % of days incarcerated in hospital	:	6.29	8.43
	Mean % of days incarcerated in jail	:	15.38	10.48
	Percentage of subjects found to be functioning well $\geq 80\%$ of all days	:	7.14	21.43

^aGroups were controlled drinker, experimental (CD-E); controlled drinker, control (CD-C); non-drinker, experimental (ND-E); and non-drinker, control (ND-C).

^bIf complete data are obtained on the one missing CD-E subject, the total mean percentage of days functioning well for subjects in this group should decrease very slightly.

^cIf complete data are obtained for one of the two missing CD-C subjects (one CD-C subject has never been located), the total mean percentage of days functioning well for subjects in this group should decrease somewhat.

^dOne ND-E subject died shortly after the completion of his first year of follow-up because of non-alcohol-related causes. If complete data are obtained for the one missing ND-E subject, the total mean percentage of days functioning well for subjects in this group should remain about stable or increase slightly.

^eOne ND-C subject died about 8 weeks after discharge, of barbiturate related causes (automobile accident, see Sobell, and Sobell, 1972).

RELEVANCE, REALISM AND EVIDENCE

Mendelson (1971) has concisely summarized the contributions of basic research to the study of alcohol dependence in the decades prior to 1960: "Our heritage from years of scientific neglect is profound ignorance concerning even the basic behavioral and biosocial concomitants of alcoholism" (p. 1681). However, this statement was not intended to imply simply that too little research had been conducted. In fact, Keller (1972a), recently found it necessary to invent a principle to summarize for posterity a large proportion of the published studies. This principle, modestly proclaimed as "Keller's Law," states that: "The investigation of any trait in alcoholics will show that they have either more or less of it" (p. 1147). Or, stated differently, "Alcoholics are different in so many ways that it makes no difference" (p. 1147). Essentially, each of these statements suggests that only a small portion of the research which currently constitutes the study of alcohol dependence has been valuable in designing effective treatment programs.

While maintaining the perspective we have developed thus far, we will now concentrate more directly on what we feel are two outstanding needs in alcohol dependence research at this time: (a) realism in accepting the results of well-conducted evaluative studies; and (b) relevance, particularly concerning an increased emphasis on designing applied treatment experiments. Despite the attention devoted to detail and consistency in developing theoretical positions, research in the field of alcohol dependence has been equally neglectful of such detail in utilizing scientific methodology. Hopefully, investigators in other areas of substance dependence research will consider the following evidence and use it to pursue more beneficial outcomes. Once again, discussion will focus primarily on alcohol dependence, and generalizations to other chemical substances may require some modifications.

It is suggested that more professionals, especially clinical treatment staff, need to have realistic attitudes with respect to the field of alcohol dependence. There are two aspects to this need: (a) acceptance of the reality of repeatedly demonstrated findings and phenomena; and (b) the ability of individuals in the field to place documented and replicated evidence above the necessity to validate personal belief systems. Certainly we are not alone in these views, as many others have incorporated these premises in their research.

In the field of alcohol dependence research there has long existed a hesitancy to accept evidence which is not consistent with generally accepted, although unsupported, theoretical positions. Partly because of this rigid adherence to theoretical positions, many relevant subject areas with respect to treating alcohol dependence and evaluating treatment outcome have been seriously neglected. The following discussion relates a few selected examples of major areas of neglected research needs or research findings in the field of alcohol dependence.

Neglected Evidence: Revisions of the Notion of Loss of Control

A critical foundation of the traditional disease concept of alcoholism, and before that an integral part of the credo of Alcoholics Anonymous, is that an alcoholic (*gamma* type, by Jellinek's classification) is affected by alcohol consumption so that: "...the ingestion of one alcoholic drink sets up a chain reaction so that they are unable to adhere to their intention to 'have one or two drinks only' but continue to ingest more and more — often

with quite some difficulty and disgust — contrary to their volition” (Jellinek, 1960, p. 41). Marconi (1959) espoused a related concept, that certain intermittent alcoholics had an inability to stop drinking after the ingestion of a small quantity of alcohol following a period of abstinence. Marconi supported his conception with some weak evidence. In an experimental test involving free access to alcohol, seven intermittent alcoholics consumed more of an ethanol solution than did six inveterate (*delta*) alcoholics theorized to suffer only from an inability to abstain (Marconi, Fink and Moya, 1967). Marconi *et al.* thus claimed to have designed a successful “. . .experimental reproduction of the ‘inability to stop’ . . .” (p. 543). Obviously, their conclusion, based on this simple procedure, is subject to a plethora of alternative explanations, as many other viewpoints would predict the same experimental outcome.

Keller (1972b) in his recent review of the development of the loss of control phenomenon concluded that, “The fascinating thing is that it should be thought necessary to devise and execute experiments to disprove a claim with no foundation at all in observed reality, as if Jellinek’s assertion in the 1952 W.H.O. report is to be taken as scientific gospel (p. 257).” However, the loss of control phenomenon is, in fact, accepted as “scientific gospel” by a great many laymen and professionals. There are both advantages to and disadvantages from entertaining a loss of control concept. The concept has very probably served to help many “arrested alcoholics” refrain from experimenting with drinking. Not as immediately apparent, however, is that the loss of control concept has had direct implications for the design of treatment programs. For instance, if certain types of alcohol-dependent individuals do have an inability to control their drinking behavior, then abstinence should necessarily be the immediate and permanent treatment goal. It is unfortunate that a study has never been conducted to estimate how many individuals faced with a lifetime prognosis of abstinence would choose not to consider themselves as “alcoholic.” For that matter, an in depth evaluation as to whether the general population would prefer to be labelled as having a “disease” as compared to having a “problem” in respect to excessive drinking has never been reported. The fact remains that while the loss of control phenomenon may currently have “no foundation in observed reality,” it does have a very real presence in the “social reality” of a great many individuals.

Considering the importance of knowing whether or not a loss of control phenomenon exists, it is not surprising to find that a number of studies have recently examined this hypothesis. Most of these studies followed the pioneering efforts of Mendelson in daring to study alcoholics experimentally in the actual presence of alcohol (Mendelson, 1964). In one of the earliest studies, Mendelson, LaDou and Solomon (1964) reported that 10 alcoholics who received up to 24 ozs. of 86-proof alcohol daily for an extended period developed no cravings for alcohol. In 1966, Merry reported a double-blind study using a within-subject design. Nine alcoholics were at times administered vitamin mixture solutions containing certain amounts of alcohol, and at other times administered the same solution containing water in place of alcohol. The results showed that subjects when administered a less concentrated or control solution reported more cravings than when the most concentrated solution was consumed.

In an investigation of the effects of self-image feedback on alcoholics, Paredes, Ludwig, Hassenfeld and Cornelison (1969) reported, as tangential findings, that consumption of one drink did not induce cravings for more alcohol in their subjects. More recently, Paredes, Hood, Seymour and Gollob (1973) concentrated directly on the loss of control phenomenon as one part of a controlled intoxication experiment. For 30 of 131 total subjects, the experimental paradigm included a drinking schedule that consisted

of two consecutive days of drinking to a maintained blood alcohol concentration of 0.14 per cent. All 131 subjects were free to discontinue the program whenever they wished. It was found that the risk of not completing the five-week program tended, in fact, to be greater for non-drinking subjects than for those assigned to the two scheduled drinking days. The authors concluded that: "The loss of control hypothesis as it is commonly understood is not supported by empirical evidence" (p. 1155). Another investigation, by Cutter, Schwaab and Nathan (1970), explored the concept of cravings for alcohol using a utility experiment. Their findings suggested that craving for alcohol among alcoholics (if it exists at all), "...is independent of any individual drinking sequence" (p. 376).

In summarizing a number of studies, Mello and Mendelson (1971) stated:

No empirical support has been provided for the notion of 'craving' by direct observations of alcoholic subjects in a situation where they can choose to drink alcohol in any volume at any time by working at a simple task. . . despite the accumulative data which are inconsistent with the notion of craving. . . this construct forms the basis for the usual therapeutic goal of total abstinence for the alcoholic patient (p. 680).

Sobell, Sobell and Christelman (1972) summarized the results of a series of studies involving experimental drinking by alcoholics. Of 214 voluntary *gamma* alcoholic subjects housed on an inpatient open ward, only 7 (3.27%) left the treatment program to seek additional drinks. Subjects participated in as many as 15 drinking sessions and on some occasions consumed as many as 16 ozs. of 86-proof alcohol. In a questionnaire portion of that study, 30 *gamma* alcoholic subjects all answered that they believed they could ingest one drink and then stop, as long as they resided in a hospital, and 90 per cent thought they would be able to stop even if they consumed 16 ozs. of liquor while hospitalized. On the other hand, 43 per cent of the same subjects thought they could consume one drink and stop if they were not hospitalized, and this figure diminished to 23 per cent when 16 ozs. was the quantity in question. The authors urged a restatement of the loss of control concept on the basis that treatment of the alcoholic "...could be facilitated by making him aware that he became drunk by his own choice, as opposed to describing him as the victim of a strange set of physiological circumstances whereby his only prognosis after the first drink was to become drunk" (p. 123).

In the same year, Engle and Williams (1972) cited 19 literature references which propounded the concept of a loss of control as being triggered by ingestion of one drink of alcohol. They then outlined 15 ineffectual attempts to provide a foundation for the presumed phenomenon. In the body of their article, they related the results of a direct test of the loss of control hypothesis using 40 alcoholic inpatients at a private hospital. Half of the subjects were randomly assigned to receive occasionally one ounce of vodka in a heavily flavored vitamin solution. The remaining half received a placebo solution. Then, a random half of the subjects in each of the groups were told they had received a solution containing one ounce of vodka. Subjects were administered a daily questionnaire evaluating their desire to drink, and on the day of the experimental manipulation all subjects were given the opportunity to request an additional drink if they developed cravings. The only subject who requested an additional drink was in the "placebo solution/told alcohol" experimental condition. They concluded that "No evidence was found for a physiological relation between one drink of alcohol and an increased desire for alcohol in the alcoholic" (p. 1103).

In more recent reports, Gottheil, Crawford and Cornelison (1973) reviewed the

experimental drinking results of four alcoholics and found little support for the concepts of cravings and loss of control. Marlatt, Demming and Reid (1973) used the guise of a taste test to obtain unobtrusive measures and found that alcoholics, told that a beverage to be tasted might contain alcohol, consumed more beverage during a session, whether or not the taste sample really contained alcohol. They reported that, "Loss of control drinking, in the form of increased consumption by alcoholics who were administered alcohol, did not occur during the drinking task" (p. 233).

Two major attempts have been made to revise the loss of control hypothesis to incorporate these experimental results. In the context of limited contradictory evidence, Glatt (1967) suggested that rather than considering loss of control as the reaction of an alcoholic to the ingestion of any alcohol, each alcoholic could be postulated to have an individualized critical blood alcohol threshold level. Loss of control would ensue if an individual's threshold was surpassed. This revision no longer seems tenable, in view of the wealth of evidence failing to demonstrate loss of control drinking by alcoholics who consumed amounts of alcohol sufficient to produce large blood alcohol concentrations (Mendelson *et al.*, 1964; Paredes *et al.*, 1973; Sobell *et al.*, 1972; Marlatt *et al.*, 1973).

A more appropriate revision would seem to be one independently proposed by Paredes *et al.* (1973), Sobell *et al.* (1972), and Keller (1972b). Apart from slight differences in phrasing, this revision suggests adding a qualifying motivational statement to the original hypothesis. Thus an individual who is an alcoholic is very likely to drink to excess after consuming an initial drink, unless for some reason he (she) does not wish to drink more or is prevented from doing so. In all of these formulations, loss of control is interpreted as an acquired process, rather than a physiologically determined one. Keller, for instance, states that, "...loss of control is a conditional symptom, arising because alcoholism is a learned process. . . (p. 164)"; and, "If and when a critical cue or signal impinges, he (*the alcoholic*) will drink and, given that he is not prevented by external circumstances, such as the unavailability of enough alcohol, he will get drunk" (p. 161, *Italics added*). In his recent article, Keller walks a mysterious path between orthodox tradition and the mounting evidence in conflict with that tradition. Thus, he first recognizes that the traditional loss of control concept is not valid, and offers a more appropriate explanation. However, he then proceeds to confuse the matter by suggesting that we recognize alcohol dependence as both a learned process and as a disease. The loss of control concept would not be dispensed with, nor even modified too severely because the concept of alcoholics without an associated loss of control, "...can cause confusion in the public mind, loss of confidence on the part of patients, erroneous jurisprudence, and misdirection of effort by government agencies" (p. 163). While Keller's motives are admirable, it may be argued that the judicial advances attained by the introduction of the disease concept are unlikely to be reversed at this time. Further, if the alcoholic is not to be viewed by the greater culture as a social deviant, one must present the facts honestly as they are determined.

*Neglected Evidence: The Ability of Some Former Alcoholics
to Drink in a Controlled or Normal Fashion*

Another commonly accepted component of both the disease concept, and the literature of Alcoholics Anonymous, is the notion that the phenomenon of alcohol dependence is

progressive and irreversible. Further drinking by an individual who has been dependent on alcohol can only lead to a greater dependence and a progression of symptoms. Simply stated: "Once an alcoholic, always an alcoholic!" A corollary is that abstinence can be the only feasible treatment objective for alcohol dependent individuals. It is probable that most individuals who are bold enough to disregard this advice are, in fact, likely to deteriorate further and thus fulfill the prophecy, especially if no treatment for the drinking problem nor training in non-dependent drinking is provided. Surprisingly, a few of the individuals who tried have not only been able to overcome their dependency without help, but were able to drink in a limited and non-dependent fashion. However, by fiat of leading professionals, these spontaneously recovered individuals were deemed never to have been "real alcoholics" at all. They were said to represent simple cases of misdiagnosis – "pseudoalcoholics" – even if this determination could never be made in a predictive fashion, but only as a *post hoc* explanation. This line of reasoning, still advanced by some of the foremost professionals in the field of alcohol dependence treatment, was best exemplified in the entourage of commentary which constituted a complete supplement to the *Quarterly Journal of Studies on Alcohol* in 1963 (Davies, 1963). The vast majority of these comments admonished Dr. D. L. Davies for simply and honestly reporting the findings of a scientifically conducted investigation of treatment outcome (1962). A full decade later, the same clarion call to battle still resounds (*i.e.*, Madsen, 1973), albeit not quite as frequently as before.

The question of whether or not some alcohol-dependent individuals can, in fact, successfully manage controlled or normal drinking without a resumed dependency is not heuristic, but can be adequately tested using sound scientific methodology. The outcome of such tests will have profound significance in defining the range of treatment modalities which may be effective in dealing with alcohol dependence. Within the context of a scientific evaluation, the traditional view that alcoholics can never drink again can be objectively validated or contradicted. To date, little objective evidence has been offered to support the traditional concept while a reasonably impressive array of evidence has been marshalled against it. The remainder of this section is devoted to a cursory review of contradictory evidence. This review is not intended to be inclusive, nor are individual studies critically evaluated. It is intended solely to demonstrate that the existing body of evidence is substantial and deals with individuals who by the traditional disease taxonomy were definitely diagnosed as "alcohol," often *gamma* (Jellinek, 1960).

There are two lines of evidence supporting the contention that some alcohol-dependent individuals can, in fact, resume moderate drinking of alcoholic beverages without suffering a loss of control. First, considerable evidence has resulted from investigations of experimental intoxication. Some of these studies were mentioned in an earlier section of this paper. A few major research projects have tended to produce most of the experimental evidence in this area. Among the more noticeable of these programs have been Mendelson and Mello's original project (Mendelson, 1964), a group in California at Patton State Hospital (Mills, Sobell, and Schaefer, 1971; Sobell *et al.*, 1972; Sobell and Sobell, 1972; 1973c), a group headed by Paredes in Oklahoma (Paredes *et al.*, 1969; Paredes *et al.*, 1973), a group at Baltimore City Hospital (Cohen, Liebson and Faillace, 1971; Cohen, Liebson, Faillace, and Allen, 1971; Bigelow, Cohen, Liebson, and Faillace, 1972; Bigelow and Liebson, 1972; Cohen, Liebson, and Faillace, 1973), and a program directed by Gottheil at the Coatesville VA Hospital in Pennsylvania (Gottheil, Murphy, Skoloda, and Corbett, 1972; Gottheil, Corbett, Grasberger, and Cornelison, 1972; Gottheil, Alterman, Skoloda, and Murphy, 1973; Gottheil *et al.*, 1973). These researchers have un-

animously confirmed that persons diagnosed as alcoholic (usually *gamma*) are capable of consuming moderate amounts of alcoholic beverages without a loss of control. Nathan and his colleagues at Rutgers University have also demonstrated similar results (Nathan, Silverstein, and Taylor, 1973).

A second impressive group of studies consists of reports of former alcohol dependent individuals successfully practising "controlled drinking," which is also referred to as "social," "limited," "moderate," and sometimes "normal" drinking. Although we will not attempt a detailed analysis of these studies here, the existence of such studies, and certain of their common characteristics are germane to the present discussion. Table II briefly summarizes some of the relevant details of 62 literature references to 59 total studies reporting that some alcoholic individuals have successfully resumed drinking. Those studies that lacked sufficient detail or contained contradictory or ambiguous evidence have not been included. Thus, a conservative perspective has been maintained.

Studies are summarized in Table II in terms of: (a) the investigator(s), year of publication, and country where the study was conducted; (b) whether or not controlled drinking (CD) was a prescribed treatment goal (R_x); (c) the duration (mos.) of the follow-up interval reported; (d) the number of subjects (N) found in each study for follow-up; (e) the number of subjects (n) practising CD; (f) the percentage of found subjects practising CD; and (g) a brief description of how each study defined CD.

The studies are grouped by two major taxonomies. The first taxonomy, the degree to which controlled drinking was specifically defined, includes three sub-categories: specific definition, vague definition, and no definition. The brief descriptions of controlled drinking included in Table II correspond fairly well with these categories. The second taxonomy classifies studies based on whether or not the reports described their subject populations as definitely diagnosed "alcoholic" prior to their participation in treatment programs. In most cases, sufficient information was provided so that subjects could be described as meeting Jellinek's (1960) criteria for *gamma* alcoholics. (Primary symptoms for this classification were reports of loss of control, physiological withdrawal reactions, or explicit references to the subjects as *gamma* type.) We used this classification system in Table II because it has often been speculated that such studies described individuals who were never really "alcoholics." More than half of the studies listed reported using chronic or *gamma* alcoholic subjects. Furthermore, it is reasonable to expect that some studies with subjects listed under "identified as 'alcoholic', but with no supporting evidence," also dealt with *gamma* alcoholics. On the other hand, subjects in some of these studies, might be more appropriately diagnosed as "problem drinkers."

In the vast majority of the studies listed, follow-up data were reported for an interval exceeding 18 months. A number of references in the literature have suggested that this is an adequate follow-up interval upon which to base reliable outcome conclusions. For instance, Selzer and Holloway (1957) have suggested that an interval of 12-24 months is adequate. Gerard and Saenger who (1966) also reviewed this literature suggested that a 12 to 18 month follow-up interval provides sufficiently reliable data on which to base conclusions. They concluded that after a 12-18 month follow-up interval, the statistical patterning of results typically remains stable, although the status of individual subjects may vary somewhat. This conclusion was based on the findings of three long term follow-up studies which were conducted in disparate locations, and utilized different criteria, patient populations and methodologies (Davies, Shepard, and Myers, 1956; Gibbins and Armstrong, 1957; Gerard and Saenger, 1959). Of particular interest, one of those studies (Gerard and Saenger, 1959) utilized an explicit follow-up category of con-

TABLE II
SUMMARY OF STUDIES REPORTING CONTROLLED DRINKING (CD)^a

Investigator(s), year and country	CD R _x ^b (yes/no)	Follow-up duration (mos)	Ss found (N) for follow-up ^c	Practicing CD		Brief description of CD
				<i>n</i>	% of <i>N</i>	
Specific definition of CD						
Ss identified as chronic or <i>gamma</i> alcoholics ^d :						
Bailey & Stewart (1967), U.S.A.	No	30-60	91	6	7	Quantity-frequency index. 2-3 drinks, twice/week.
Baker, <i>et al.</i> (1972), U.S.A.	Yes No	1½ 1½	19 9	3 N.D. ^c	16 N.D.	≤ 12 ozs of 86-proof liquor/2 days.
Barr, <i>et al.</i> (1973) U.S.A.	No	11-34	456	14	3	“A beer every week or so.”
Bolman (1965), U.S.A.	No	12-84	14	2	29	1-2 glasses of beer less than once/ month.
Cain (1964), U.S.A.	No	36+	36	19+	42+	1-2 drinks after work or at parties.
Davies (1962), G.B.	No	84-132	93	7	7	Maximum of 3 pints of beer/day.
Davies, <i>et al.</i> (1969), G.B.	No	60-324	4	4	100	1-2 pints of beer or 1-2 shots of whiskey/weekend.
deMorsier & Feldmann (1952), France	No	17-64	430	76	18	Occasional glass of beer or wine with meals.
Glatt, (1967), G.B.	No	24	30	1	3	1-2 beers/day.
Kendall (1965), U.S.A. (also, Kendall & Stanton 1966)	No	36-96	62	4	6	1 glass of sherry, to 2 pints of beer/day.

Lazarus (1965), S. Africa	Yes	14	1	1	100	≤ 2 glasses of beer, wine, or hard liquor/day.
Nathan, <i>et al.</i> (1973), U.S.A.	Yes	2-2/3	3	1	33	A BAC level ≤ 0.08%.
Pattison, <i>et al.</i> (1968), U.S.A.	No	18-24	36	8	22	Drinking status scale; CD=1-6.
Schaefer (1972), U.S.A. (Follow-up of Mills, <i>et al.</i> (1971)).	Yes No	12 12	E ^f =10 C ^g =11	4 0	40 0	≤ 6 ozs of 86-proof liquor or equiv. in alcohol content/day.
Selzer, & Holloway (1957), U.S.A.	No	72	83	13	16	From 1-2 beers/day, to 6-12 beers/ weekend.
Sobell, & Sobell (1972; 1973c,d), U.S.A.	Yes No No No	12 12 12 12	CD-E ^h =20 CD-C ^h =19 ND-E ^h =15 ND-C ^h =15	11 ⁱ 2 ⁱ 2 ⁱ 1 ⁱ	55 11 13 7	≤ 6 ozs of 86-proof liquor or equiv. in alcohol content/day.
Sobell, & Sobell (1973b), U.S.A. (Follow-up of Sobell, & Sobell, 1972, 2nd year results).	Yes No No No	24 24 24 24	CD-E=19 CD-C=18 ND-E=14 ND-C=15	13 1 3 2	68 6 21 13	≤ 6 ozs of 86-proof liquor or equiv. in alcohol content/day.
Ss identified as "alco- holics," but no support- ing evidence provided:	Yes	18	27	10	37	Rarely exceeding a BAC level of 0.07%.
Caddy (1972a), Aus- tralia. (Follow-up of Lovibond, & Caddy, 1970).	Yes	6-12	60	19	32	Rarely exceeding a BAC level of 0.07%.

Table II—Continued

SUMMARY OF STUDIES REPORTING CONTROLLED DRINKING (CD)^a

Investigator(s), year and country	CD R _x ^b (yes/no)	Follow-up duration (mos)	Ss found (N) for follow-up ^c	Practicing CD		Brief description of CD
				n	% of N	
				Specific definition of CD		
Gerard, <i>et al.</i> (1962), U.S.A.	No	24-96	299	41	14	2-3 beers daily, or on rare occasions.
Gerard, & Saenger (1966), U.S.A.	No	12	618	35	7	2-3 beers daily, or at social functions.
Kraft, & Al-Issa (1967), G.B.	No	15	1	1	100	Occasionally drank a half pint of beer.
Kraft, & Al-Issa (1966), G.B.	No	6-9	2	2	100	Occasionally drank a half pint of beer.
Lovibond, & Caddy (1970), Australia	Yes	4-60	28	21	75	Rarely exceeding a BAC level of 0.07%.
Marlatt (1973), U.S.A.	No No	3 3	E=52 C=13	9 1	17 8	Alcohol intake of ≤ 50 gms/week.
Mukasa, & Arikawa (1968), Japan	Yes	1-72	330	220	67	≤ 100-200 ml of Sake (30 proof)/day.
Mukasa, <i>et al.</i> (1964), Japan.	Yes	3-48	250	96	38	≤ 100-200 ml of Sake (30 proof)/day.
Shea (1954), U.S.A.	No	60	1	1	100	2 bottles of beer or 2 glasses of wine/ day.

Sobell, & Sobell (1973a), U.S.A.	Yes	5+	3	3	100	≤ 6 ozs of 86-proof liquor or equiv. in alcohol content/day.	
	No	5+	3	1	33		
Vague definition of CD							
Ss identified as chronic or <i>gamma</i> alcoholics ^d :							
	Barchha, <i>et al.</i> (1968), U.S.A.	No	12	N.A. ^j	9	14	Marked reduction and no associated problems.
	Bhakta (1971), Australia.	No	12	20	7	35	Moderate drinking with no adverse effects.
	Goodwin, <i>et al.</i> (1971), U.S.A.	No	96	N.A. ^j	17	N.A. ^j	Drinking 1-10 times/month, and rarely intoxicated.
	Gottheil, Murphy, <i>et al.</i> (1972), U.S.A.	No	6	23	12	52	Moderate drinking and not intoxicated.
	Harper, & Hickson (1951), G.B.	No	24-60	80	16	20	Consumed small quantities, or only one relapse.
	Mills, <i>et al.</i> (1971), U.S.A.	Yes No	1½ 1½	E=13 C=13	2 0	15 0	Occasional drinking without drunken- ness.
	Räikköläinen & Turunen (1969), Finland.	No	12-240	71	6	8	Reduction and less potent drinks.
	Reinert & Bowen (1968), U.S.A.	No	12	156	4	3	Drinking with others, and no loss of control.
	Tomsovic (1970), U.S.A.	No	12	175	13	33	Drank occasionally with no associated problems.
	van Dijk & van Dijk- Koffeman (1973), Netherlands.	No	30-66	200	20	10	Intake minimal with no drunkenness.

Table II—Continued

SUMMARY OF STUDIES REPORTING CONTROLLED DRINKING (CD)^a

Investigator(s), year and country	CD R _x ^b (yes/no)	Follow-up duration (mos)	Ss found (N) for follow-up ^c	Practicing CD <i>n</i>	% of N	Brief description of CD
Vague definition of CD						
Ss identified as "alcoholics," but no supporting evidence provided:						
Lemere (1953), U.S.A.	No	N.D.	500	14	3	Amount and degree abated to normal drinking.
Pfeffer, & Berger (1957), U.S.A.	No	12	60	7	12	Fewer binges and less daily drinking.
Schuckit, & Winokur (1972), U.S.A.	No	25-50	45	11	24	Drank moderate amounts socially with no associated problems.
No definition of CD						
Ss identified as chronic or gamma alcoholics ^d :						
Blake (1965), Scotland.	No	6-12	27	1	4	"Drinking in a controlled manner."
Dubourg (1969), G.B.	No	16-26	76	3	4	"Resumed controlled social drinking."
Ewing (1973), U.S.A. (Also Ewing, & Rouse, 1972).	Yes	13-29	6	3	50	"Doing well."
Faillace, <i>et al.</i> , (1972), U.S.A.	No	6	24	3	13	Global adjustment rating of 7 or better.

Lundquist (1973), Sweden.	No	108	200	40 ^k	20	Occasionally consumed small quantities of alcohol.
Moore, & Ramseur (1960), U.S.A.	No	3-144	91	5	6	“Well-controlled social drinkers.”
Pokorny, <i>et al.</i> (1968), U.S.A.	No	12	88	23	26	“Resumed controlled ‘social’ drinking.”
Ss identified as “alcoholics,” but no supporting evidence provided:						
Anant (1968), Canada.	No	24+	N.D.	1	N.D.	Able to “take alcohol occasionally; stop at will.”
Evans (1965), G.B.	No	3-43	100	6	6	Managed to control their drinking.
Hacquard, <i>et al.</i> (1960), France.	No	24+	124	18	15	Drank moderately of alcohol and with meals.
Knott, Beard, & Fink (1972), U.S.A. (See, “One of seven. . .”)	No	N.D.	4,000+	≤400	≤10	Resumed drinking with controlled imbibing.
Lambert (1964), Sweden	No	N.D.	100	9	9	Able to drink liquor in moderation.
Miller (1972), U.S.A.	Yes	6	1	1	100	“Moderate drinking pattern established.”
Monnerot (1963), France.	No	6-12	338	56	17	“Ingesting drinks but moderately.”
Nørvig, & Nielsen (1956), Denmark.	No	33-63	156	57	37	“Moderate drinking (with) no overindulgence.”
Pattison, <i>et al.</i> (1969), U.S.A.	No	12-200	45	4	9	“Limited drinking. . . maintaining control.”

Table II—Continued

SUMMARY OF STUDIES REPORTING CONTROLLED DRINKING (CD) ^a						
Investigator(s), year and country	CD R _x ^b (yes/no)	Follow-up duration (mos)	Ss found (N) for follow-up ^c	Practicing CD		Brief description of CD
				<i>n</i>	% of <i>N</i>	
				No definition of CD		
Quirk (1968), Canada.	No	24+	2	2	100	“Taking occasional social drinks.”
Robson, <i>et al.</i> (1965) Canada	No	10-46	153	N.D.	N.D.	A large number. . . “Managed to control their drinking.”
Rohan (1970), U.S.A.	No	2-30	108	1-23	1-21	“May have been improved or practicing controlled drinking.”
Rosengren (1966), Sweden.	No	1-12+	105	23	22	Moderate liquor intake without relapsing.

^a Controlled drinking is a summary term used to describe what others have also referred to as "limited drinking," "moderate drinking," "social drinking," or "normal drinking." The specific definitions of such drinking vary from author to author.

^b Treatment of controlled drinking prescribed.

^c The sample size found for follow-up (*N*) refers only to subjects for whom complete follow-up data was reported, as well as deceased subjects.

^d Subjects either met Jellinek's (1960) criteria as *gamma* alcoholics or closely paralleled the chronicity of *gamma* alcoholics.

^e Not determinable from evidence reviewed.

^f Experimental subjects.

^g Control subjects.

^h See Figure 1 for definition of experimental conditions in Sobell & Sobell study.

ⁱ Controlled drinking for this study was defined as functioning well (abstinent or controlled drinking days) for greater than 80% of the interval, plus an "Improved" rating in either Vocational Status or Collateral Evaluation.

^j Not applicable.

^k Lundquist, personal communication, 1973.

trolled drinking and compared subjects at two, five and eight years after intake into a treatment program.

While the major item of importance in Table II is the reported incidence of controlled drinking, a number of qualifications apply when interpreting this tabular presentation. First, the Table summarizes only the reported incidence of subjects performing controlled drinking. Almost all of the studies contained additional information about the incidence of abstinent subjects, but for brevity we have not included these figures. Second, the criteria used to determine the number of subjects practising controlled drinking (n) for each study were purposely conservative. If a study included information from the interviewers or from collateral sources that appeared to contradict subjects' self-reports of controlled drinking, those subjects were not reported as part of the controlled drinking group (n). Third, most studies did not provide substantial data about the longitudinal patterns of controlled drinking, such as when and how the patterns were acquired, whether the subjects were occasionally able to drink to drunkenness, the frequency of occasions during the follow-up report period when the subject had practised controlled drinking. Lastly, it must be noted that only a few recent studies used a specifically stated treatment objective of controlled drinking. Thus, since subjects in the majority of studies had abstinence treatment goals, the reported results were often both surprising and perplexing to their authors. More importantly, these authors cannot be accused of finding treatment outcomes to match their preconceptions.

With respect to all treatment evaluation studies, some probing questions may now be considered. First, how many studies have failed to report some incidence of successfully controlled drinking because of insufficient procedures or inadequate dependent variable measures? Perhaps certain drinking behaviors are only reported if they are measured with appropriate treatment evaluation measures (*i.e.*, questions about controlled drinking). The studies in Table II, as all treatment outcome studies in the field of alcohol dependence research to date, share varying degrees of deficient methodology often because more satisfactory procedures and measures have not yet been developed.

Table II contains references to a body of literature which has frequently been neglected or ignored by researchers and other professionals in the field of alcohol dependence. The implications of this evidence seem clear. First, if we wish to have a realistic perspective then we must accept the validity of some of the findings, in particular, the finding that at least some alcoholics have the potential to drink in a controlled manner after treatment. Having then accepted the possibility of controlled drinking, we should direct our efforts towards generating information that would help predict which kinds of treatment objectives might be appropriate for various types of alcoholics. Second, this evidence is directly relevant to the construction of alcohol dependence treatment programs. If alternative treatment objectives to abstinence are not recognized, some alcohol-dependent individuals will quite possibly be denied an efficacious treatment. Given the present evidence, we suggest that it is both appropriate and justifiable to recognize alternatives to abstinence as legitimate treatment objectives for some alcohol-dependent persons, always remembering that controlled drinking is probably no more or less likely than abstinence to be attained simply through self-commitment. Also, the concept of striving toward controlled drinking could be highly detrimental, should an individual use this to justify continued abusive drinking. Therefore, for the present time such treatment goals should only be pursued as the target of specifically designed treatment programs.

Before leaving this topic, we give a final caution. Just as the feasibility of this goal has been too easily dismissed in the past, so controlled drinking might be too readily

accepted as a panacea now or in the future. It is but a short step from agreeing that the pursuit of controlled drinking is a legitimate enterprise, to relying again on the traditional medical model and referring to such an outcome as a "cure." The relative efficacy of treatment objectives will only be determined by clinical research and will, very probably, be found to be highly dependent upon individual case histories and circumstances. We suggest that controlled drinking be considered as a treatment goal in the same way that any other behavior changes might be considered the fulfillment of treatment goals.

It is seldom the case that an individual becomes permanently abstinent simply as a result of treatment, and when a patient experiences a "slip," this does not imply that the treatment goal of abstinence should be discarded. Similarly, a person treated with controlled drinking objectives may at times reacquire excessive drinking patterns, and if he should "slip," it does not necessarily mean that a change in treatment goal is indicated. Other than making treatment goal decisions for an individual patient at a specified point in time, and taking into account that person's existing intrinsic and extrinsic environments, the question of the relative efficacy of abstinence as compared to controlled drinking is, in our opinion, a moot point.

Neglected Methodology: Measures of Treatment Outcome

While serious methodological deficiencies and inadequacies pervade alcohol dependence treatment outcome studies, it would not be fair to say that the topic of such neglect has been ignored. For instance, four excellent review articles which comprehensively evaluated studies spanning a period of 63 years (1909-1971) have pointed up the lack of competent and sophisticated methodological approaches and evaluation procedures in these alcoholism treatment studies (Voegtlin and Lemere, 1942; Hill and Blane, 1967; Miller, Pokorny, Valles, and Cleveland, 1970; Crawford, Chalupsky, and Hurley, 1973). The consensus of these articles is that major deficiencies occur along all dimensions of treatment methodology, ranging from pre-treatment measures to the final interpretation of results. In their reviews, the above authors cite the following examples of inadequate treatment evaluation: (a) inability to trace a large proportion of subjects; (b) unreliability of treatment outcome measures; (c) unequal follow-up intervals across subjects; (d) inadequate follow-up techniques; (e) poor or non-reported descriptions of follow-up search procedures; (f) inadequate definition of criterion variables; (g) lack of supporting collateral information to substantiate subjects' self-reports; (h) lack of multiple treatment outcomes measures; and (i) inappropriate data analysis and presentation of results. These reviews were unanimously critical of the "state of the art" in alcohol dependence treatment outcome research. Unfortunately, even with repeated acknowledgement of grossly inadequate methodology in published research, very few studies have suggested, much less implemented, changes in this methodology.

Since previous reviews provide outstanding summaries of the general deficiencies of treatment evaluation procedures, we will focus on more recently recognized problems in this area of alcohol dependence research. These problems have become evident for two major reasons: (a) the recent inception of controlled drinking as an alternative treatment goal to abstinence; and (b) a careful examination and evaluation of the utility and validity of the disease concept. The disease concept, discussed in detail earlier, has certain necessary implications for treatment goals and ways of measuring treatment outcome. For example, since the disease concept portrays the alcoholic as incapable of controlling his

(her) drinking, then the drinking behavior of "alcoholics" can be viewed as either sober (abstinent), or drunk. This dichotomous and erroneous representation has typically been used to measure drinking behavior in treatment outcome studies with alcoholics. Further, since in this view the alcoholic has great difficulty in stopping drinking once started, there is even less reason to believe that he is capable of experiencing any successful controlled drinking days. Thus, in cases where such behavior does occur, it is likely to be regarded as the beginning phase of loss of control drinking.

However, the massive body of evidence already reviewed in this paper strongly suggests that traditional conceptions are naive and perhaps detrimental to the advance of progress in alcohol dependence research. In the discussion to follow, only selected examples of deficiencies in treatment evaluation will be cited. While these deficiencies will be referenced by a limited number of studies, a plethora of supporting evidence is readily available from the literature. Even in the rare instances when relatively adequate treatment outcome measures and procedures have been used, there still remain serious problems with interpreting results.

An important area of neglected treatment evaluation concerns the highly observable and quantifiable behavior of alcohol consumption. Since excessive drinking is the reason most individuals enter treatment programs, the effectiveness of such programs should certainly be evaluated with respect to measures of drinking behavior. Traditionally, treatment programs have only used one treatment goal for drinking, namely, abstinence (Wall and Allen, 1944; Moore and Ramseur, 1960; Soren and Thomas, 1970; Kish and Hermann, 1971). Moderate drinking by alcoholics has been of little concern to those in charge of treatment programs whose goal is abstinence. The dichotomous representation of post-treatment drinking behavior appears to be accepted frequently as axiomatic, since many studies do not describe in any detail what they mean when reporting subjects as "drunk" or "drinking" other than nondescript categories such as "heavy drinking," "occasional slips," "drunk," "improved drinking" or "relapses" (Walton, Ritson, and Kennedy, 1966; Vogler, Lunde, Johnson, and Martin, 1970; Kish and Hermann, 1971). We suggest that traditional treatment conceptions and orientations in the field of alcohol dependence have restricted and hampered the development of appropriate and more sophisticated measures of follow-up and treatment evaluation, particularly with respect to drinking behavior.

One suggested alternative dependent variable for evaluating drinking behavior is a measure of *daily drinking disposition*. Using such a measure, the investigators collect data for each day of a follow-up interval, recording the specific quantities and types of any alcoholic beverages consumed. Subjects should not know the taxonomic categories used to encode the drinking behavior data. Such a procedure helps prevent subject demand characteristics from operating. For coding drinking behavior, it is suggested that daily drinking disposition data be trichotomized into categories of: (a) *abstinent days* (no drinking of alcoholic beverages); (b) *controlled or moderate drinking days* (amount or definition of appropriate drinking for alcohol dependent individuals is presently a question for discussion); and (c) *drunk days* (consumption of any amount exceeding the agreed upon definition of controlled drinking). To date there is only one published study (Sobell and Sobell, 1972) which uses a measure of specific daily drinking disposition. Additionally, an experimental treatment program in progress at Mendota (Wisconsin) State Hospital is using similarly obtained follow-up dispositions, referred to as "time-line drinking measures."⁴

⁴Personal communication, Dr. Leonard Stein, 1973.

In order to evaluate the outcome of a treatment program appropriately, a representative sample of the patients treated should be evaluated for post-discharge functioning. However, Rhodes and Hudson (1969), among others, have noted the difficulty of locating and maintaining contact with subjects for an extended period of time. In most of the treatment outcome studies reviewed by Hill and Blane (1967), Miller *et al.* (1970), and Crawford *et al.* (1973), the proportion of cases lost for follow-up typically ranges between 20 per cent and 50 per cent. Recently, Pittman and Tate (1972) reported a follow-up study where data were retrieved on 94.8 per cent of all subjects. They reported this as, "...the highest proportion attained in any systematic alcoholism follow-up study reported to date (p. 185)." The authors' own work has reported follow-up rates of 98.6 per cent for the first year of follow-up (Sobell and Sobell, 1973d), and 94.3 per cent during a second year of follow-up (Sobell and Sobell, 1973b). Unfortunately, the number of published studies with retrieval rates greater than 90 per cent is extremely limited. Pittman and Tate (1972) suggest "...that considerable skepticism should be attached to any follow-up study with a retrieval rate of *less than* 90 per cent (p. 185)." As the percentage of subjects found for follow-up decreases, severe limitations arise with respect to evaluating the effectiveness of a treatment program. For instance, if a subject cannot be traced for a follow-up, it means in all probability a high degree of geographical movement, poor social and vocational stability or lack of official records and therefore indicates that the person is likely to be functioning poorly. If this is the case, group results are likely to be skewed in the direction of good outcomes when a substantial number of patients are lost to follow-up. Miller *et al.* (1970) have provided a good demonstration of the manner in which the reporting of incomplete follow-up results can bias outcome conclusions. In considering the same point, Hill and Blane (1967) have stated: "It is not clear whether the bias introduced by low follow-up rates is systematic or random, although it may be argued that systematic bias occurs insofar as patients who are located and followed are probably those who have benefitted from treatment (p. 93)."

One reason many subjects are lost to follow-up may be an artifact of follow-up procedures — specifically, the frequency of follow-up contacts. Follow-up contacts have typically been impersonal, of limited duration, and occurred months or years after subjects were discharged from a treatment program. Prior to the time of follow-up contact, subjects have had little reason to keep in touch with the investigators, nor to monitor their own level of functioning. This "shotgun follow-up" procedure (Nørvig and Nielsen, 1956; Davies, 1962; Gerard, Saenger, and Wile, 1962; Pattison, Headly, Gleser, and Gottschalk, 1968) involves interviewing subjects after they have been discharged from treatment for a pre-specified criterion period of time, usually twelve months to five years. There are three serious problems with this kind of follow-up procedure: (a) as the follow-up interval lengthens, it becomes increasingly difficult to locate subjects; (b) as the follow-up interval lengthens, the reliability of subjects' reported data becomes more questionable due to memory deficiency; and (c) when a subject is interviewed regarding a long follow-up period, the results or evaluation derived may not be generalizable to the entire period, as the subject may be reporting data only for the immediate interval prior to the actual interview — forgetting or distorting earlier events. A preferred alternative over this widely used technique is to maintain frequent follow-up contacts, thereby shortening the interval for which data are gathered and simultaneously obtaining multiple behavior samples of each subject's functioning.

From the evidence presented thus far, tracking subjects and their collaterals and collecting adequate follow-up data may seem to be impossible. Hill and Blane (1967)

attribute low follow-up rates to faulty techniques, usually based on a lack of personnel or funds, or "...on the widely held conviction that alcoholics are more difficult to follow than other groups (p. 94)." Realistically, follow-up does take a good deal of time and persistence. However, with a certain amount of preliminary caution before subjects are discharged from treatment, the chances of locating subjects and their being cooperative with interviewers can be increased. First, it would be advisable to brief subjects carefully about the nature of the contacts to be made and reasons for conducting follow-up, how and when they can expect to be contacted, and the kind of question they can expect to be asked. Further, to better ensure that subjects are not lost to follow-up, a sufficient number of collateral sources of information (friends and relatives) who might have knowledge of the subject can be obtained prior to discharge. Additionally, as will be discussed later, these persons can be interviewed to check for accuracy and consistency of the subjects' self-reports. If a certain amount of care and caution are taken prior to a patient's discharge, more complete and reliable follow-up results are ensured (Chafetz, Blane, Abram, Golner, Lacy, McCourt, Clark, and Meyers, 1962; Sobell and Sobell, 1972; 1973b, c, d).

Another area of concern is the validity of subjects' self-reports. Drinking behavior has been measured almost solely by self-report in treatment outcome studies. It is only recently that the reliability of such measures has been queried. Can an alcoholic's self-reports about drinking be believed and if so, when? Such questions are important and basic to the interpretation of outcome studies whatever the treatment goal, but very few studies have investigated the parameters involved. The self-reports of alcohol-dependent individuals can be investigated for their validity and reliability by interviewing a number of collateral sources of information. While this kind of validation can further strengthen the treatment outcome results of a study, many studies have not employed any collateral sources of information (Bowen, and Androes, 1968; Tomsovic, 1970; Faillace, Flamer, Imber, and Ward, 1972). Generally, collaterals include friends, relatives, employers, spouses, and neighbors. In addition to this type of verification, access to certain official records is often available (*i.e.*, jail, hospital, welfare, driver's records) to corroborate subjects' reports. One further procedure to better evaluate drinking disposition is random in-field probes of subjects' blood alcohol levels (by breath samples).

Drinking behavior, however, is only one measure of post-treatment functioning. Pattison *et al.* (1968), among others, have suggested that treatment evaluation in alcohol dependence research should include multiple treatment outcome measures. Essentially, their evidence suggests that improvement in one area of life functioning does not necessarily imply or predict improvement in other areas of life functioning. Unfortunately, there is a scarcity of alcohol dependence research studies reporting multiple measures of treatment outcome. It is probable that whole ranges of measures to deal with critical areas of treatment outcome have yet to be developed, much less evaluated.

A final and perplexing consideration with respect to evaluating treatment outcome, supposing a wealth of adequate measures to exist, is an inability to interpret the resulting data appropriately. One reason is that pre-treatment baseline data are lacking in most studies. However, even if such data were available, it could be argued that the period preceding treatment is likely to be selectively biased toward poor functioning, and thus a pre- and post-treatment comparison would not be appropriate. Lastly, with reference to controlled drinking data, it even becomes difficult to draw other than arbitrary and conservative inferences about how such drinking approximates "normal drinking," as few population norms have been reported.

Even this brief and selective review of the "state of the art" has demonstrated profound and neglected problems for measuring treatment outcome. As a result, the field of alcohol dependence research suffers from a paucity of appropriate follow-up procedures and measures of treatment outcome to adequately evaluate treatment programs. Currently, attention has been drawn to these neglected problems, but the field of treatment evaluation appears to be, at the best, in its infancy.

CONCLUSIONS: PROSPECTS FOR A USEFUL SYNTHESIS

In conclusion, there are three matters which deserve further discussion. First, with reference to the study of alcohol dependence only, it is becoming increasingly clear that earlier conceptualizations and conflicts over theoretical accuracy have hindered some attempts at achieving a better understanding of the entire syndrome. Rossi and Nathan (1969) have made a similar point:

There is a growing belief among investigators that conceptualizing alcoholism as a singular rather than a plural phenomenon has been a major reason for the relatively small increment in our understanding of the determinants of alcoholic drinking in comparison to the amount of research conducted. . . it would be more fruitful to employ the plural alcoholisms rather than the singular alcoholism in conceptualizing strategy for research in this area (p. 318).

Considering the abundance of problems associated with the study of alcohol dependence, we feel that significant progress would be made by an effective synthesis among disciplinary approaches and among investigators. Some of the more useful and relevant aspects of such a synthesis might include: (a) allowing for interchange among various orientations in an atmosphere which is conducive to innovation; (b) stressing the need for utilization of scientific principles in developing and evaluating applied alcohol dependence treatment programs — the concept of operational assumptions may provide a useful alternative in advancing theoretical positions; (c) realistic conceptualizations, and a climate where demonstrated phenomena are accepted as facts needing explanation; and (d) primary emphases upon a task orientation; immediate relevance; and adaptive functions for the alcohol dependent individual.

The second matter concerns the relevance of the history of alcohol dependence research for investigators of other substance dependencies. The critical issues are extremely salient. Professional rigidity hinders progress and innovation. The long-term consequences of sacrificing scientific methodology and concept development for expediency simply do not warrant such an approach.

The final topic involves striving for an agreeable conceptualization or definition of "dependency." Levy (1963) in discussing the value of psychodiagnosis, stated the following:

Psychodiagnostics is a descriptive venture, having as its ultimate goal the provision of a basis for the anticipation of the behavior of the patient under various contingencies. Unless it can be shown that this goal is accomplished by the use of a particular psychodiagnostic approach, continued use of that approach is sheer ritual. (p. 157)

Similar considerations apply to evaluating the merits of investing substantial efforts in

pursuit of an agreeable definition of the term *dependency*. Unless the resultant definition can be expected to have functional utility (*i.e.*, adding to knowledge or allowing us to deal better with matters which would otherwise escape our attention), then it, too, may simply constitute an exercise in professional ritualism. In the field of alcohol dependence, it appears that searching for commonalities has, as one side-effect, led to a detrimental state of rigidity. The possibility exists that over-emphasizing the need to discover commonalities among the various substance dependencies could result in diminishing the potential for diversity in the field of substance dependence research. Currently, the authors feel that such a limited perspective would not only be premature, but would hinder progress, and should therefore be avoided.

SUMMARY

This paper, focusing on alcohol dependence as an example of substance dependence, addresses certain general issues which require serious consideration. The history of alcohol dependence research, especially theory development, has demonstrated many peculiarities. An understanding of these anomalies can be valuable to investigators of other substance dependencies.

Evidence is reviewed which suggests that traditional conceptualizations of alcohol dependence, despite their original utility, have impeded the development of innovative treatment approaches and hindered progress in understanding and dealing with this syndrome. A number of factors have contributed to the present rigidity: (a) sacrificing scientific methodology and concept development for political expediency; (b) public and professional reification of theoretical relationships lacking factual bases; and (c) an apparent unwillingness by many professionals to deal realistically with objective evidence in conflict with traditional conceptions.

An alternative procedure for advancing various theoretical positions is proposed. This procedure preserves the benefits of theory development while minimizing destructive conflict. To maximize research progress, it is suggested that investigators explicitly acknowledge the foundations of their inquiries as "operational assumptions." The difference between "operational assumptions" and "theories of etiology" does not concern the content of a given position, but rather the orientation and expectations of investigators. Emphasizing the assumptive basis of one's research cogently communicates the non-definitive nature of a theoretical position and provides a caveat against both reification and allowing personal beliefs to interfere with the objective evaluation of findings. An example of research utilizing "operational assumptions" is presented and discussed.

Excessive allegiance to theoretical positions lacking a material foundation (*i.e.*, some aspects of traditional conceptions) has also had serious consequences in terms of disregarding conflicting evidence and neglecting issues relevant to developing more effective treatments. Typically, treatment programs and evaluation techniques have been based on the widely accepted, although scientifically unsupported, disease concept of alcoholism. An abundance of studies contradicting some traditional notions of alcohol dependence — loss of control, and irreversibility — are reviewed. This evidence strongly indicates that loss of control does not occur in a literal sense, and that some alcoholics are, in fact, capable of resuming drinking in a controlled manner without untoward consequences (59 separate follow-up studies are cited in documentation.) A realistic perspective and willingness to deal with *all* documented phenomena is prerequisite to encouraging relevant applied research. At this time, it is suggested that alternatives to abstinence be recognized

as legitimate and respectable treatment objectives for some alcohol dependent individuals, and that more research be oriented toward exploring the implications of such a change.

Evaluation techniques and measures of treatment outcome have similarly been victims of limited theoretical conceptualizations. Even with repeated acknowledgement of grossly inadequate methodology in most published outcome research, very few studies have either attended to these deficiencies or implemented changes. However, recent developments in applied alcohol dependence research are compelling a reformulation of evaluation measures, procedures, and interpretation.

Regardless of etiology, alcohol dependence appears to be a complex syndrome involving varying degrees of physical, psychological and social complications. Considering the current "state of the art" in alcohol dependence research, it is suggested that a useful synthesis embracing disciplinary approaches and investigators could significantly accelerate progress. Characteristics of such a synthesis might include: (a) encouraging interchange among various orientations; (b) an atmosphere conducive to innovation; (c) emphasizing the need to incorporate scientific principles in applied research; (d) a realistic perspective where demonstrated phenomena are accepted as findings needing explanation; and (e) an increased emphasis on applied research.

Lastly, the usefulness of pursuing a mutually agreeable definition of the concept of "dependency" is considered. It is proposed that such a pursuit has limited value unless the new definition either adds to our current knowledge or allows us to be cognizant of matters which we would otherwise not recognize.

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Concluding Remarks

Harold Kalant

Concluding remarks, at a symposium of this type, probably serve primarily a ritual function, not unlike the laying of a cornerstone after the building is completed. Indeed, like some present-day cornerstones, concluding remarks may even have hidden away inside them a small sampling of to-day's wisdom, which readers in some distant future might dig out and look at with amusement, or perhaps with surprise that we should have had such glimmerings of insight, given the primitive state of our knowledge! However, these concluding remarks will certainly not contain any microfilm-like recording of all the ideas that were expressed during this symposium. They will be nothing more than one person's purely subjective impression of the main themes that were discussed here, as seen from the vantage point of a reasonably detached observer who was not directly involved in the debate.

For whatever they may be worth, these observations might be some reflection of the state of the art, particularly in comparison with the other symposia that have been taking place here at the same time. It is rather informative to see what kinds of concluding, even if not conclusive, remarks one can use to describe a conference, according to the area of investigation that is being discussed. I had an opportunity, last week and this, to listen extensively to three different conferences: one on alcohol and liver damage; one on alcohol, drugs and brain damage; and this one on tolerance and dependence. They form a rather interesting spectrum of states of the art, if you will.

The alcohol and liver damage symposium, which reflected the results of half a century or more of studies on the effects of alcohol on the liver, permitted a certain number of fairly definite conclusions. It was possible for the participants to agree that certain lines of research that were followed in the past have proven to be unproductive

and can be dropped. Certain factors which were investigated extensively in the past, we see now to be at best partial factors. From one decade to another the emphasis in research has shifted from one to another aspect, and we can now begin to have fairly clear perspectives about their relative importance.

The brain damage symposium was at the other end of the spectrum because there was not even a suggestion of agreement on the fundamental terms to be used. People could not define satisfactorily what is meant by "brain damage". The term "organicity", as applied to a set of behavioral signs, seemed to bear no discernible correlation with demonstrable histological or chemical change in the brain. I think that the inevitable concluding remarks, if there had been any there, would have been that our first task is to agree on what we mean by brain damage, and then go back and find better ways of looking to see whether there is any.

The present conference falls somewhere between the other two. We can probably agree that there really are certain phenomena which are clearly designated by the terms "dependence" and "tolerance". We may not agree on the relations between them, but at least we know there is something there to be investigated, and we are at the stage of talking about mechanisms and possible approaches to intervention. Of the topics that came up in the discussion of the various papers, I would personally select perhaps three or four as main themes that recurred in different presentations, and in different ways. These themes are perhaps the best indicators of the present state of our knowledge and concepts of drug dependence.

The first of these themes is well expressed by Nancy Mello's appeal for a definition of the problems in terms which permit experimental testing. This was echoed in the papers by the Sobells, and by Peter Nathan. As they and others pointed out, though we agree that there is a global phenomenon designated "dependence" to be investigated, we cannot really investigate it effectively until we can subdivide it into components which lend themselves to controlled examination. During the discussion, some one commented: "This symposium is very depressing because it reveals a lot of things that we should have done two years ago and, for one reason or another, did not." Undoubtedly one of those lamented "things" was the job of defining the phenomena in terms of separate components which can be investigated experimentally. This task really is critical, because of constant problems of tautology in our terms and concepts. There is a danger that we may define phenomena in terms of the investigational techniques used to study them, and then turn around and make assumptions, based on those definitions, about what the underlying mechanisms must be, when the range of possible mechanisms which can be investigated is inherent in the selection of techniques.

This question of appropriate definition of problems was raised again in the papers of Miriam Cohen and the Sobells, in which they touched on the prominence of *a priori* assumptions in the formulation of questions for clinical and behavioral research. The concepts of craving and loss of control provide choice examples of the type of circular reasoning which has long hampered effective research. To explain why an alcoholic who has already experienced damaging effects of alcohol would resume drinking despite his own better judgment, it was convenient to invent the concept of "craving". The return to drinking was then taken as evidence for the existence of this postulated craving. A comparable example of the vicious circle is provided by the concept of "loss of control". Rarely, if ever, does an individual become an alcoholic on first contact with alcohol. There is typically a history of moderate or "controlled" drinking, which at some point changes into a pattern of repeated or sustained heavy drinking. The same is usually true if

the person reverts to drinking after a period of abstinence. When this happens, the person is described as having loss of control; this descriptive term is invoked to explain the supposed impossibility of enabling an alcoholic to become a "normal drinker". In a *reductio ad absurdum*, this means that a name used to describe a behavior is also the mechanism causing the behavior.

Terms such as craving and loss of control appear to have been given their formal discharge, at least by the participants in this symposium if not by the world at large. There seemed to be, here, a consensus that these terms are no longer tenable. Control of drinking was clearly demonstrable *under certain conditions*, even by patients who had what would have been previously defined clinically as loss of control in their natural environment. The question, then, is not whether the control is permanently lost, but rather, why it occurs under some circumstances and not under others. How can one attempt to make therapeutic use of circumstances under which it does occur? What determines the development of intake levels beyond those which the patient is in fact, under certain circumstances, capable of controlling?

The question of individual differences has by no means been ruled out. This is something which one attempts deliberately to exclude for analytical purposes in many experimental situations. Yet Jim Woods' evidence indicated that perhaps 30 to 40 per cent of animals will self-administer intoxicating amounts of ethanol while others will not. The same animals which will do it intravenously will, under spontaneous conditions, not do it orally. These findings draw attention to the importance of individual differences; the importance of the types of effects which can be produced upon the nervous system, as determinants of behavior in one set of conditions and not necessarily in others; the importance of gustatory stimuli; and the importance of rate of change of blood alcohol level. The same direct pharmacological actions of alcohol itself may evidently give rise to markedly different subjective cues or different behavioral responses in different animals, according to the modifying influences of various constitutional or environmental factors. Clearly, there is much research to be done yet, along the lines which Peter Nathan spoke about, attempting to correlate the internal cues produced by drugs with the control of drug-related behavior. We do not yet know how this occurs in the normal individuals, let alone whether the control mechanism does or does not change in people whose drug taking behavior is defined empirically as abnormal, or how the changes can be therapeutically reversed.

Another main theme of the symposium has been the relation between physical dependence and the broader picture implied by the term drug dependence. The discussions here suggest that there has been a marked lessening of the confusion which plagued concepts for many years. Most investigators seem to have agreed, if I am correct in my assessment of the discussions, that since physical dependence is a consequence of chronic drug use, it can in no sense be invoked as a primary causal mechanism. Once established, it may contribute to the *maintenance* of a set of behaviors; this fact has importance for therapeutic intervention, but it is clearly not the most fruitful ground in which to search for underlying causes. Perhaps one of the main sources of difficulty has been the tendency, exemplified by the definitions formulated by the W.H.O. Expert Committee on Drugs of Dependence, to think of drug dependence as a *state* or *condition*. At the risk of some challenge, I would suggest that we should really stop talking about drug dependence as a condition, and should instead describe it as a behavior. We have heard from several of the speakers that drug dependence is defined by the ingestion, under a variety of conditions, of varying amounts of drugs which produce certain changes in the organism. Those

changes, which give rise to tolerance and to withdrawal reactions (physical dependence), may be defined as a condition, but the primary problem is a behavior.

In order to investigate dependence scientifically, then, we must define satisfactorily the behavioral criteria, and then determine the factors that influence them, their relations to the type and amount of drug, and the biochemical or functional alteration of tissues which accompanies them. As orthodox materialist scientists, we assume that changes in cellular functions in the brain must underlie behavioral alterations. Some one said, in another context, "I am not aware that anyone has ever shown a behavior in the absence of a brain". One of the problems to date has been a concentration of research effort on the cellular changes which accompany the development of physical dependence, rather than those which correlate with the development of dependence as defined behaviorally. A start has been made in the latter direction, but there is still a huge gap between the biochemical alterations and the behavioral changes which precede, accompany and conceivably follow the development of them. We can still talk only of "biochemical correlates of dependence", a term with which Roger Russell first acquainted me. Our biochemical or physiological studies of drug dependence can at best reveal concomitant phenomena, and we have yet to establish the exact relation of these to the basic behavioral alterations.

A major question that was raised explicitly during the first day of discussion, and subsequently by implication at least, is the reversibility of tolerance, and of dependence in both behavioral and physiological aspects. This was highlighted in the presentations by Dora Goldstein and by Eugene LeBlanc concerning studies with alcohol, and Avram Goldstein's experiments with opiates. The differences, both in findings and interpretations, are great enough to preclude any definitive conclusions for some time to come. The papers presented data which appear to indicate radically different patterns of acquisition and loss of tolerance and physical dependence — so different, indeed, as to suggest quite different underlying mechanisms. Yet the discussion left a number of obvious unanswered questions. Is the difference really one of rate rather than of the maximum final level attainable? Is there a species difference in the kinetics, rather than in the fundamental nature of the process under study? A true convulsive syndrome can be demonstrated easily as part of an alcohol withdrawal reaction in the mouse, but only with great difficulty in the rat. Is this merely the reflection of a species difference in rates of acquisition and loss of adaptive changes in the nervous system, relative to the rates of build-up and loss of drug concentration? Can this in turn determine that there is an apparent carry-over of adaptation from one drug exposure to the next in the one species and not in the other? The question was raised about the role of conditioned withdrawal symptoms in the carry-over model which LeBlanc proposed, but then one might ask, why was it not present also in the Goldsteins' models?

The answer perhaps lies in the criteria which are chosen for the demonstration of tolerance and dependence. We need not assume identical half-lives, identical rate terms, for all the components of the total complex of adaptations and de-adaptations that can occur during exposure to and withdrawal from a drug. It is, therefore, not necessary *a priori* to expect that if one picks different criteria, one will find the same set of kinetics. Here, obviously, is an area of considerable investigation over quite a time to come. I think it bears out the same point that was made in the brain damage conference, to wit, that in this type of work we should probably not limit ourselves to a single test. The definition of subtle minimal changes, the identification of underlying processes, and the establishment of correct temporal sequences become more and more realistic, the more dis-

tinguishably different criteria of change we use. Here again we must avoid *a priori* assumptions about what it is we are looking for, and such assumptions are inevitable when we pick a single criterion of change. Even if we can not state it explicitly, the choice of a single test must correspond to some preconception we have about the nature of the underlying processes that we are examining.

The role of physical dependence in the overall process of drug dependence has been clarified in a number of respects. From the papers presented by Gerhard Freund and by Dora Goldstein, it is clear that we now have available a variety of animal models of alcohol withdrawal seizures, the convulsive states which constitute one clear-cut component of alcohol withdrawal reactions. Jack Mendelson described a series of important endocrine and peripheral tissue changes which accompany the development of physical dependence, and which can evidently contribute to the total picture of the withdrawal reactions. Various behavioral and pharmacological techniques can now be used to accelerate the development of such phenomena, or to demonstrate them more clearly or with different dosage ranges. This should permit us to compare the gross signs of physical dependence with a variety of biochemical and physiological changes under a range of different kinds of challenge, or presentation of the drug. In that way we can hopefully try to pick out some set of cellular changes, or in the ideal case some single change, bearing the closest temporal relationship with the developing pictures of dependence. This might give us some clue to the cellular sites at which to look for the truly fundamental adaptive changes.

On the other hand, Jim Woods' findings emphasized again the relatively small difference between rates of drug-oriented responding behavior by animals with physical dependence as a consequence of prolonged drug administration, and the rates of drug self-administration developed in the *absence* of demonstrable physical dependence. This indicates that physical dependence is probably a secondary factor, secondary not only in terms of time sequence but also in terms of importance in controlling the rate of drug self-administration. This takes us back to the clinical studies by Miriam Cohen, and the Sobells, which demonstrated that repeated development of tolerance and physical dependence did not prevent the subjects from exercising a very clear demonstrable measure of control over their alcohol intake. Again we are forced to the conclusion that physical dependence is a phenomenon which is important as a therapeutic problem, which has importance over a limited time for the wellbeing of the patient, and which may have importance under defined environmental and behavioral circumstances for the maintenance of certain types of behavior, but which probably is not central to the question of altering the behavioral patterns that constitute the essence of drug dependence.

The symposium has also made clear that we are still some distance away from an explanation of the cellular mechanisms of physical dependence. Avram Goldstein's presentation of his beautiful work with the myenteric plexus will be dear to the heart of almost any pharmacologist, because it permits one to define in precise cellular and quantitative terms the nature of a specific component of the adaptive changes produced by exposure to opiates. Yet here again, one would have to recognize that there is a big gap between the change found in the isolated tissue and the picture of physical dependence as one sees it in the intact organism. The types of procedure which are required, to separate a defined and clearly recognizable set of cells that can be studied under *in vitro* conditions, automatically preclude the examination of possible modulating factors which, in the whole organism, must inevitably contribute to the response. This is the kind of problem we still face in all of the biochemical and physiological studies in this field.

Between them and the behavior of the whole organism there is still a very large gap to bridge. That is a truism which is repeated in every conference of this type, yet the fact that it is a truism does not make it any less true.

The last major theme that I would comment on, and which was discussed extensively, is the question of which kinds of therapeutic research can be based upon our present concepts of dependence. Even an admittedly organically oriented pharmacologist, such as I, can say with a clear conscience that drug dependence is primarily to be defined as a behavior. If behavioral concepts are invoked to explain the development of drug-taking behavior of sufficient intensity to give rise to definable problems, why should behavioral principles not be applied in the investigation of therapy? The point was brought up that there are certain vested interests, preconceptions, and political and social influences which determine what is considered acceptable research or acceptable treatment goals. Scientists who work not in a circumscribed scientific atmosphere, but in a setting in which social expectations and social priorities determine to a very large extent the encouragement or discouragement given to research, must clearly take this into account.

This gives me an opportunity to raise a matter which is not a direct outgrowth of this conference, and is perhaps not even germane to it, but which nevertheless should be of importance to all of us: the type and degree of social responsibility of the scientist who works in a field which is of clear social relevance and concern. Most of us would probably agree that we have a social responsibility, but there are obviously widely differing views among us, as to what role that should cause us to assume. My personal view is that we have a responsibility to inform our fellow citizens as objectively as possible about the present state of knowledge concerning drug dependence, and also about the implications of that knowledge for the various options that may be open with respect to treatment and to social policies. But I believe that it is neither our responsibility nor our right *as scientists* to attempt to direct society toward one or another specific policy.

I am sure we all agree that society has an interest in the types of behavior which are shown by its members with respect to drug use, and that it is the society at large which defines the "problems". It is obvious that different societies may define the same behavior as a problem or not a problem, according to how that behavior matches the expectations and norms of each society. Therefore, we have a responsibility to explain what we know about the factors which generate drug using behavior, about the influences which determine the extent of such behavior, about the probable consequences of that behavior, as well as those of different types of intervention, about what we do *not* yet know in these respects, and what we have to do to find out. But when it comes to determining which of the policy alternatives the society should adopt, we must recognize that we have reached the limits of our role as scientists, and are then talking as members of the society on an equal footing with the others. Our duty as scientists is clearly to discover and to inform, but our participation in the social decisions is then as citizens and not as scientists, and our personal values, ideologies and ethics have no claim to pre-eminence merely because of our scientific knowledge. To come back to the opening note of these concluding remarks, in formulating without preconceptions the questions that we ask as a basis for investigation, perhaps we also have to define for ourselves the limits of our own competence and expertise with respect to the social implications of our own findings.

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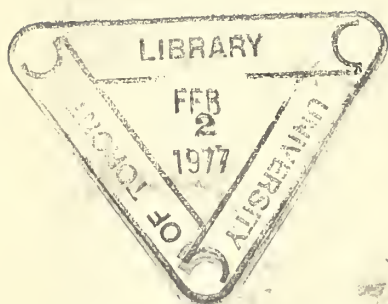
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